Hospital Library

OCT 20 1930

PHYSIOLOGICAL REVIEWS

EDITED FOR

THE AMERICAN PHYSIOLOGICAL SOCIETY

CONTENTS

	PAGE
TRANSPLANTATION AND INDIVIDUALITY. *Leo Loeb*	547
ADRENAL INSUFFICIENCY AND RELATED CONSIDERATIONS. *S. W. Britton*	617

VOL. X, No. 4

Issued October, 1930

BALTIMORE, U. S. A.

Entered as second-class matter, January 15, 1921, at the Post Office at Baltimore, Md., under the act of March 8, 1879

Made in United States of America

PHYSIOLOGICAL REVIEWS

PHYSIOLOGICAL REVIEWS is owned and controlled by the American Physiological Society. It is edited by a board appointed by the society consisting of:

W. H. HOWELL, Baltimore
LEO LOEB, St. Louis
J. J. R. MACLEOD, Aberdeen, Scotland
A. J. CARLSON, Chicago
P. A. SHAFFER, St. Louis
TORALD SOLLMANN, Cleveland
D. R. HOOKER, Managing Editor, Baltimore

The Editorial Board selects the subjects and authors of all articles which are published, the aim being to provide concise but comprehensive reviews of the recent literature and present status of various subjects in Physiology, using this term in a broad sense to include Bio-chemistry, Bio-physics, Experimental Pharmacology and Experimental Pathology. Each volume will consist of from sixteen to twenty articles, making a total of about five hundred pages per volume. The numbers will be issued quarterly in January, April, July and October of each year.

Subscriptions will be received in advance only. The subscription price is:

$6.00 per volume in the United States, net postpaid
$6.25 per volume in Canada, net postpaid
$6.50 per volume elsewhere, net postpaid
$2.50 per single number, net postpaid

Subscriptions should be sent to

D. R. HOOKER, *Managing Editor*
19 W. CHASE STREET, BALTIMORE, MD.

Contents of Volume X, 1930

M. L. ANSON AND A. E. MIRSKY: The Hemoglobin Compounds, with Special Reference to Protein Chemistry and the Significance of the Heme Pigments in Tissue Oxidations

J. H. BURN: The Errors of Biological Assay

H. E. MAGEE: The Physiology of the Small Intestines

E. D. ADRIAN: The Action of the Sense Organs

LEO LOEB: Individuality and Transplantation

V. E. HENDERSON: The Present Status of the Narcosis Theories

W. F. VÒN OETTINGEN: Excretion and Distribution of Bismuth Compounds

S. W. BRITTON: Adrenal Insufficiency

DAVID RAPPORT: The Interconversion of Foodstuffs

R. A. MCCANCE: The Chemistry of the Degradation of Protein Nitrogen

HERBERT S. GASSER: Contracture of Skeletal Muscle

HARDOLPH WASTENEYS AND HENRY BORSOOK: The Enzymatic Synthesis of Protein

A. C. IVY: The Rôle of Hormones in Digestion

PHYSIOLOGICAL REVIEWS

VOL. X OCTOBER, 1930 No. 4

TRANSPLANTATION AND INDIVIDUALITY

LEO LOEB

Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

By transplantation we understand the complete or partial separation of a piece of tissue, or of a part of an organ, or of a whole organ, from its normal connection and its transfer to a different place, either in the same individual (autotransplantation), or in a closely related individual (syngenesiotransplantation), or into another, not directly related individual of the same species (homoiotransplantation), or into an individual belonging to a different species or class of animals (heterotransplantation, in the wider sense). The joining together of two organisms also may be considered as transplantation.

Transplantations have been carried out in animals as well as in plants, in unicellular and in multicellular organisms, in adult and in embryonic organisms. Furthermore, transplantations have been carried out by different investigators from different points of view. It is the aim of the surgeon to find methods by which he can cover defects in the body, or supply a deficiency in function, through transplantation. The biologist and, in particular, the experimental embryologist use transplantation as a method to determine how far development takes place by self determination and how far it is dependent upon variable environmental factors. The physiologist, by means of transplantations, determines the function of organs and of the specific substances which they produce, while for the pathologist transplantation serves as a method for the analysis of certain growth phenomena, in particular of regeneration and hypertrophy, for the study of the origin of certain types of cells and of the relation of normal growth to tumor growth.

In the course of investigations such as those mentioned, it was observed, casually at first, that not all animals, in which pieces were transplanted, were equally suitable as hosts and, in particular, surgeons, like Thiersch and Ollier, as early as in the second half of the last century, noticed that autotransplantations succeeded best and thus Thiersch and

others suggested that different species and even different individuals might somehow differ in their chemical constitution. However, it is only relatively recently, namely, within the last 25 years, that the great importance of the relationship between host and transplant, as a factor which determines the fate of the transplant, has been recognized in its full significance and that the connection between genetic constitution of host and donor of the graft and the fate of the transplanted tissue was analyzed quantitatively. Moreover, it was only in the last 15 or 20 years that this method was used conversely for the analysis of the factors which distinguish individuals, strains and species. Thus transplantation has become an instrument for the analysis of individuality. It is solely with this aspect of transplantation that we are concerned in this review and it will be necessary to limit ourselves in the main to a description of transplantations carried out in adult mammals, although we shall have occasion to refer to some experiments done in lower adult vertebrates.

As stated above, the studies of various investigators, having primarily different objectives, at first as a matter of chance provided data which could be used in the solution of the problem of individuality. Gradually this problem developed into a central motive towards which converged the studies of various biological sciences. Biologists like Naegeli, Hertwig, Giard and others made early contributions; in particular did they notice a parallelism between morphological characters and phylogenetic relationship on the one hand, and transplantability on the other hand, and furthermore a certain parallelism between hybridizability and transplantability. More recent investigations provided fuller data as to gradation in transplantability and as to its relation to embryonic differentiation. From a biochemical point of view, Huppert, Hamburger, Abderhalden, Obermayer and Pick, Landsteiner, Heidelberger, Osborne and Wells, Gortner and others approached the problem of species differences. Among geneticists it was especially Correns who attempted to correlate the data of genetics with those of transplantation. Of interest in this connection is also the study of blood groups and of the heterogenetic antigens of Forssman. Likewise the application of the methods of immunology for the determination of the graded relationships between antigens, in various species of animals and plants, and the study of the parallelism existing between these relationships and the exchange of tissues between these species by transplantation provide data and viewpoints, which are of value for our study. Lastly the investigation of the laws underlying transplantability of tumors, as

compared with those which are valid in the case of normal tissues, adds further important facts.

In this review it will not be possible to consider all these aspects and ramifications of the central problem with which we are concerned. We shall, in the main, have to limit our discussion to a consideration of certain series of transplantations, which were specifically undertaken with a view of analysing individuality. They were carried out in higher organisms, in which the individual differences are most pronounced; higher organisms are therefore best suited for such an analysis. We shall thus be able only casually to refer to other aspects of this problem and, in particular, to studies concerned with lower organisms and with tumors.

We believe that we can introduce the problem best, by describing briefly certain types of transplantations in which the relationship between host and donor differed in different cases. We can thus state the methods and the criteria used in the analysis of individuality by means of transplantation. The experiments to which we refer were mainly carried out in guinea pigs and rats and, as a routine, thyroid gland and cartilage were transplanted simultaneously from donor to host in each case; these we considered as representative tissues; but in some series we included, also, transplantations of other organs.

Autotransplantation. If we make an autotransplantation of the thyroid gland, the peripheral part remains alive, while the insufficiently nourished central portion becomes necrotic and, if it is large, is at first converted into a dense fibrous material through the ingrowth of connective tissue of the host; if it is small, a loose, more or less myxoid connective tissue takes its place. In the living, peripheral part, as well as in the adjoining portion of the central necrotic zone, there develops a satisfactory supply of blood vessels, whereas the fibroblasts grow in in only a moderate amount and do not form dense fibrous tissue. Gradually vessels and some fibroblasts grow also into the central fibrous mass and absorb it. It is possible that, in addition, a part of this fibrous material is pushed out into the surrounding tissues. Thus we found usually within three weeks, the central fibrous knob replaced by a small amount of relatively loose, well vascularized connective tissue, and the acini around it well preserved, merely surrounded by vessels and some connective tissue cells without any formation of dense fibrous tissue; more and more the transplant assumes the character of the normal thyroid gland. There are slight differences in the behavior of such autotransplants in the guinea pig and in the rat, which in part at least correspond to differences between the normal glands in these two types

of animals. Thus while, as stated, in the guinea pig the zone between the peripheral glandular and the central fibrous part is well vascularized and usually represents more or less loose myxoid connective tissue, in the rat this intermediate zone is less prominent.

Homoiotransplantation. The results are considerably different after homoiotransplantation. In this case the fibroblasts grow in greater numbers into the central necrotic part and form a dense mass of fibrous tissue, which is larger than in early stages of autotransplantation and which adjoins directly the peripheral glandular zone. Moreover in homoiotransplants this central fibrous material persists. Furthermore, the fibroblasts grow also around the living acini of the peripheral zone, forming a dense fibrous tissue around them which presses on the acini and causes a shrinkage and gradual obliteration of their lumen. Fibroblasts may also invade the acini and thus destroy them directly. But soon an additional, very characteristic change takes place: beginning about the seventh or eighth day following transplantation, there develops a remarkable infiltration of the transplant by lymphocytes, which surround and invade the living tissue, often overwhelming it, and thus help to destroy it. Conditions are very different in autotransplants where we may find, in the first few weeks following transplantation, a few lymphocytes here and there; these are usually attracted by some abnormal material, which may be found in the early stages in or around any type of transplants. But soon, in this case, regulatory processes take place which lead to the elimination of such substances; the very small collections of lymphocytes disappear altogether, and after a short period these cells are no more frequent in autotransplants than in the normal gland. As to the relative vascularization of homoio- and autotransplants, we find it much less in the former. Usually the homoio-graft is completely destroyed 20 to 30 days following transplantation, but in some instances, in rats, it survived this critical period and was at least partly preserved after about two months; presumably we had in such cases to deal with transplantation in related animals.

If we compare, with the behavior of the thyroid gland, that of a much more resistant tissue, namely, cartilage together with the adjoining fat tissue, we find in principle the same reactions as in the case of the thyroid; but there exist some quantitative differences. In autotransplants the tissues soon return to the state of the normal cartilage and fat. In homoiotransplants, on the other hand, connective tissue invades the fat tissue and largely replaces it, while in those areas where fat tissue remains preserved, giant and epithelioid cells develop, usually much

more extensively than after autotransplantation. Directly around the homoiotransplanted cartilage there forms, as a rule, a thick layer of fibrous tissue, which is infiltrated with collections of lymphocytes and these latter occur at various other points, especially around blood vessels which are found in the remnants of the fat tissue or in the fibrous tissue that replaced it. However, the cartilage itself remains largely preserved after homoiotransplantation, although isolated parts of it may perhaps become necrotic; connective tissue and lymphocytes have not usually the power to penetrate into living cartilage, but they may penetrate into areas where it has become necrotic. Thus, cartilage usually remains alive after homoiotransplantation and this is due to the mechanical properties of this tissue which make it more resistant. Still, certain parts of cartilage are less resistant, especially the large cartilage cells which adjoin the bone; these usually perish after homoiotransplantation, while they may be preserved after autotransplantation. In addition to the mechanical factors, which are responsible for a better preservation of homoiotransplanted cartilage, there is noticeable a diminished attraction of lymphocytes by cartilage and fat as compared with thyroid and various other tissues. This observation applies especially to the rat, but to a less extent also to the guinea pig.

We see then that, after autotransplantation, certain tissues may remain alive permanently, as for instance thyroid gland, fat tissue and cartilage, but after homoiotransplantation, the majority of these tissues are preserved for only a short time. However, regenerative processes may take place under both conditions; thus, mitoses are found in the homoiotransplanted, as well as in the autotransplanted, acinus cells of the thyroid gland, and in transplanted cartilage the perichondrium may proliferate and form new cartilage at points where the transplant has been cut, as well as around necrotic areas of cartilage tissue. But regenerative processes are, as a rule, more extensive in autotransplants than in homoiotransplants.

Transplantation into different varieties. If, instead of transplanting tissues to another animal of the same species and variety, we transplant thyroid into animals of a different variety, as for instance from white to hooded, or to a certain inbred strain of yellow rats, we obtain essentially the same results as after ordinary homoiotransplantation, but the reactions are more accentuated. Thus, in this case, the reaction of the connective tissue and of the lymphocytes against the transplant is especially active and after 20 days the transplant is completely destroyed, or only small, damaged parts of it are left. In cartilage and fat transplan-

tation, the reaction is likewise severe. The replacement of fat tissue by fibrous tissue, as well as the epithelioid and giant cell reaction in the transplanted fat, is more complete in this type of transplantation than after ordinary homoiotransplantation; also the lymphocytic reaction is usually stronger. In cartilage necrosis is more extensive, while in bone marrow necrosis and replacement by fibrous tissue are more complete and rapid. Though regeneration on the part of the perichondrium is not entirely prevented, under these conditions, it is more restricted and may assume some abnormal characteristics. There is therefore noticeable, in these cases, a parallelism between the distance in relationship and the intensity of the injury inflicted on the transplant.

Syngenesiotransplantation. If, instead of increasing the distance in relationship between donor and host, we diminish it, and exchange tissues between brothers and sisters, or between parents and children, we find an interesting change in the mode of reaction on the part of the host against the transplant. This type of transplantation may be designated as syngenesiotransplantation. In a typical case, the behavior of the host towards the transplant may, in the first period following transplantation, be similar to that shown towards an autotransplant. It is the connective tissue and vascular reactions which take place in the early periods of transplantation, during the first week and early part of the second week, which largely determine the structure of the transplant. These reactions are similar to those observed after autotransplantation, and the structure of a typical syngenesiotransplant is therefore similar to that of an autotransplant. But, at a later period, disharmonies between transplant and host develop, and it is now especially the lymphocytic reaction which manifests itself. At a relatively late date, perhaps as late as 40 days after transplantation, a thyroid transplant, that so far has been approximately like an autotransplant, gradually becomes invaded by lymphocytes, which enter first the septa between the acini, then the acini themselves, and in the end overwhelm them. At last, the transplant may almost resemble a lymph gland, so densely is the tissue permeated with lymphocytes. The graft may thus be destroyed. In the later stages a slight activity on the part of the connective tissue may accompany the lymphocytic reaction. In addition to a condition of this kind which is especially instructive, because it allows a fairly sharp separation between the connective tissue and vascular reactions on the one hand, and the lymphocytic reaction on the other hand, we may find, in syngenesiotransplantation, transitional stages between the conditions found in autotransplantation and those observed in homoiotransplanta-

tion, according to the varying degree of genetic relationship between host and donor.

Other tissues behave correspondingly in syngenesiotransplantation. Thus syngenesiotransplanted fat and cartilage tissue may resemble autotransplanted tissue, except that there is a slight increase in lymphocytic infiltration and in connective tissue in the transplant. In principle the reactions are the same in all kinds of tissues, but there are found in different tissues quantitative differences, similar to those which we have demonstrated in thyroid, cartilage and fat tissues.

Different tissues show a variation in the power of resistance to injurious conditions of numerous kinds, and among them we must include those unfavorable conditions which develop after transplantation into not nearly related individuals. Furthermore, there seem to exist differences in the intensity with which different tissues elicit reactions on the part of the host. Among those tissues which show resistance, or against which the reaction is less intense, we find in addition to cartilage and perichondrium, the periosteum, the ovary, and, to some extent, skin. On the other hand, the resistance is slight in the case of bone marrow, the myxoid subepithelial connective tissue of the uterus, liver, spleen, adrenal tissue; other tissues, such as kidney and parathyroid, behave in a somewhat similar way to thyroid. Of course, in organ transplants, the different constituent parts also show a very different power of resistance. Thus, in the ovary, the simple epithelial ducts, the germ epithelium and the interstitial tissue are more resistant, while the corpus luteum and the large follicles perish very readily. Furthermore, after transplantation, we have not only to consider the survival of the transplant, but also the recovery of tissue which was injured directly as the result of the operation, but which subsequently may recover if conditions are favorable. For instance, the unstriated muscle tissue of the uterus may recover from early injury after autotransplantation, and in favorable cases of syngenesiotransplantation, but it does not usually do so after a homoiotransplantation. In addition, we have to consider the regenerative growth processes which take place in the transplant under favorable conditions and which are inhibited under unfavorable conditions; the genetic relationship between host and donor largely determines the outcome of these processes. It is necessary to estimate all these factors in evaluating the reaction which takes place between host and transplant.

Heterotransplantation. If, instead of transplanting tissues within the same species, we transplant them from one species to another, the results

differ in various respects from those obtained after homoiotransplantation. In the case of tissues which are not very resistant, like thyroid, kidney, bone marrow, and even skin, the direct injury to the transplants, inflicted evidently through the body fluids of the host, is so great that they show marked degenerative changes towards the end of the first and during the second week, before the connective tissue and lymphocytic reaction has had a chance fully to develop. There may, during the brief period of survival, still be some slight mitotic activity in living cells, but it is diminished as compared with the mitotic activity of homoiotransplants. Only in certain cases, in which such a tissue happens to survive for a little longer time, it may call forth a somewhat stronger connective tissue reaction in the periphery. If, however, we use for heterotransplantation a somewhat more resistant tissue, like cartilage, together with the surrounding fat tissue, it will remain preserved for a longer period and under these conditions the connective tissue and lymphocytic reactions develop very intensely around the graft, and gradually these reactive host tissues may also penetrate into the heterotransplant. But in this case also, an apparently direct injurious effect on the part of the body fluids of the host is noticeable, the necrotic areas being more extensive in the heterogenous as compared with the homoiogenous cartilage, and after about 4 weeks the necrosis becomes complete. In addition, no perichondrial regeneration occurs after heterotransplantation. Furthermore, it is of interest to note that around and in the heterotransplanted tissue not only lymphocytes but also polymorphonuclear leucocytes may collect, although usually they are present only in small numbers. In auto-, syngenesio- and homoiotransplants these latter cells are absent, except in the first few days following transplantation, when accidental injurious processes connected with the operation may attract them. Also in the case of other heterotransplanted tissues, very marked injurious effects are observed; thus striated muscle does not show the regenerative reactions, which we may see after homoiotransplantation, and bone marrow soon becomes totally necrotic and is replaced by fibrous tissue.

In the majority of the tissues mentioned, the injurious effects of heterotransplantation are always so intense that there is little chance for the observation of differences in reaction, which may be graded in accordance with the near or distant relationship of host and donor. However, there are some indications, also in heterotransplantation, that such differences do exist and that grafting into more related species is somewhat less injurious than grafting into distantly related species. More-

over transplantations into different classes of animals seem, on the whole, to be more injurious than those into the same class, and W. Schultz maintains that the results of transplantation are more favorable, if tissues are exchanged between species that can be hybridized than between non-hybridizable species.

Transplantation of lens of eye. The lens of the eye differs from other tissues in that it shows organ-specificity while its species-specificity is apparently not fully developed. It was therefore of interest to test the behavior of lens tissue after auto-, homoio-, and heterotransplantation. M. S. Fleisher, who carried out such experiments, found that homoioreactions against lens tissue were lacking, but that there was a distinct heteroreaction, as evidenced by an increased activity of polymorphonuclear leucocytes around the transplant, an increase in the fibrous character of the surrounding connective tissue, a deficient vascularization of this fibrous tissue and an early destruction of the lens epithelium. It is probable that the capsule surrounding the lens exerts a slight protection against the injurious effects of the heterogenous host; it is possible also that the homoioreaction, which is of a much more delicate character than the heteroreaction, does not become manifest, because the protective influence of the capsule is, in this case, more effective. It is of interest furthermore that the marked lymphocytic reaction, which is absent around heterotransplanted kidney, thyroid and certain other tissues, but which is quite marked around heterotransplanted cartilage, is lacking also around the heterotransplanted lens, probably because, in this case likewise, the action of the heterogenous tissue ceases to be effective at a relatively early date. These experiments seem to indicate that species specificity exists in the lens, as well as in other tissues.

Multiple transplantations. If, instead of transplanting one piece of tissue, we transplant different kinds of tissues, or several pieces of the same kind of tissue, simultaneously from one donor into the same host, we find that, as a general rule, all the pieces behave in a corresponding way; they show the reaction characteristic of the relationship between host and donor. Of course, we must remember in this connection that different tissues show a different degree of resistance to the reactions of the host and elicit the reaction with different intensity. We also have to consider accidental factors, which may influence the result. If we take these variables into account, our findings in this respect are in accordance with expectation. On the other hand, if we transplant into the same host, at the same time, pieces from different donors, the reaction against the tissue of each donor, on the part of the host, is in accord-

ance with the specific relationship between that particular donor and the host; we have to deal with localized reactions, which differ around each piece, in accordance with the character of the individual donor. Thus we obtain confirmatory evidence for the conclusion stated above, that it is the relationship between host and donor which essentially determines the kind and intensity of reaction against the transplant.

Theory of organismal differentials. We may assume that all or almost all the tissues of an individual, within a certain species, have, in common, certain chemical characteristics, which may be designated as individuality differential; in a similar way, all the tissues of near relatives, of different strains, varieties, species, genera and classes of animals have, in common, chemical characteristics, which may be designated as syngenesio, strain, variety, species (hetero), generic, and class differentials. These differentials determine the reaction between donor and host. We may characterize them, in general, as organismal differentials, in contrast to the organ and tissue differentials, which latter differentiate specific organs and tissues within the same organism and which may be similar in corresponding organs in different individuals and species. An organ or tissue within the same organism, which has the same organ or tissue differential as the corresponding organ or tissue of another individual of the same species, differs from the latter in its individuality differential, while it has the same individuality differential as a different tissue or organ belonging to the same individual. Inasmuch as we find all possible gradations of relationship between donor and host and correspondingly all possible intensities and kinds of reactions, each one shading into the neighboring one, we may compare this graded series of organismal differentials and the corresponding reactions to a spectrum and designate it as the spectrum of differentials and reactions to differentials.

After transplanting a piece of an organ into a near relative of the donor, or into an unrelated individual of the same species, or into an individual belonging to a different species, the individuality differential is no longer adapted to its environment and it acts as a syngenesio-, homoio-, hetero- differential, respectively. In this inadequate environment the individuality differentials assume injurious properties, either directly or after interaction with the body fluids of the host, the differentials thus becoming transformed according to the relationship between host and donor into syngenesio, or homoio, or heterotoxins. It is towards these toxins that the host tissue responds. The lymphocytes are attracted, the vascular supply is diminished and fibroblasts are stimulated to greater activity; these latter cells invade the transplant in

greater number and undergo more readily secondary changes, leading to the formation of an excess of fibrous tissue which largely replaces the graft. As to the action of the lymphocytes, there can be no doubt that they actually help to destroy the transplant. This is quite clear in many cases of syngenesiotransplantation, in which the transplant is apparently quite normal, until it becomes more and more invaded and at last overwhelmed by lymphocytes; these, like a hostile army, advance in dense masses and entirely destroy the tissue which is slightly strange to them. Up to the point where they have penetrated, the tissues appear normal; behind them there is destruction. This injurious action, exerted by the lymphocytes, is also quite evident in case thyroid tissue, after homoiotransplantation, undergoes compensatory hypertrophy; here we may see clearly that the lymphocytes invade living, and apparently healthy cells. It is largely by means of these cellular reactions on the part of the host tissues, which the homoiotoxins set into motion, that the destruction of the homoiotransplants is accomplished. However, there are some indications that, in addition, homoiotoxins may possibly exert a direct injurious effect on certain more sensitive tissues like the myxoid connective tissue which is found underneath the uterine epithelium, at certain stages of the sexual cycle, and to some extent also on the uterine unstriated muscle tissue and on the bone marrow. Furthermore, some abnormalities in pigmentation, which appear after syngenesio- or perhaps even after homoiotransplantation of pigmented skin into a defect in white skin, in the guinea pig, and which are lacking after autotransplantation of such skin, may be due to the direct rather than the indirect action of syngenesiotoxins or homoiotoxins. It is possible, also, that the interference with the regenerative power of certain tissues, like the perichondrium, which we observe after transplantation into different varieties of some species, may be due to a direct action of the organismal toxins developing under these conditions. The direct injurious action of homoiotoxins is suggested by the fact that the injury to the more sensitive tissues may occur very early after transplantation, at a time when the local action of connective tissue and lymphocytes has not yet become very pronounced. However, there still remains the remote possibility that also these injuries are only the indirect effects of the lymphocytes and of the excess formation of fibrous tissue interfering with the nourishment of the more sensitive parts of the transplant.

In this connection we may mention that the toxins, thus developed, not only inhibit, directly or indirectly, regenerative processes, but also the growth processes caused by specific agencies. Thus processes of

compensatory hypertrophy, which take place readily in autotransplanted thryoid gland, may to some extent be inhibited, although not entirely prevented, after homoiotransplantation. Similarly in the homoiotransplanted uterus, experimental deciduomata cannot be produced as readily as in the autotransplanted uterus; this reaction, leading to the formation of deciduomata, occurs so soon after transplantation, that a direct effect of homoiotoxins may be assumed with some probability.

Much more definite is the direct injurious action of the body fluids on the graft after heterotransplantation. Thus the heterotoxins injure directly and very intensely epithelial tissues, which, after homoiotransplantation, suffer in the main as a result of the aggressive action of the surrounding host cells. But even in case of heterotransplantation, gradually a very pronounced connective tissue and lymphocytic reaction develops around more resistant tissues, which are not directly injured by the heterotoxins; and when these reactions have appeared, it is very difficult to determine how much of the further injury, inflicted on the graft, is due to the direct action of the heterotoxins and how much is due to the secondary reaction on the part of the host cells. There is a further difference between the syngenesiotoxins and the homoiotoxins, on the one hand, and the heterotoxins, on the other hand, in that the former are relatively mild and lead, as a rule, only to the mobilization of the lymphocytes, which latter may appear without any preceding necrosis of the host tissue, whereas the heterotoxins not only mobilize the lymphocytes but also attract the polymorphonuclear leucocytes, which, as stated, are almost always in evidence around heterotransplants, although not always in large numbers. We know, in general, that polymorphonuclear leucocytes appear under conditions in which we have to deal with the acute and intense action of injurious substances, while lymphocytes react to disturbances of a less acute and less intense character. The fact that the former kind of cells is present around heterotransplants, but not around homoiotransplants, may therefore be taken as indicating that heterotoxins have a more severe effect, are more injurious than homoiotoxins; a conclusion which agrees with the other observations mentioned above. The heterotoxins differ from the homoiotoxins in still another respect. While the homoioreactions appear, as far as we know at the present time, only around living and therefore metabolizing transplanted tissue, the heteroreactions appear even around dead, not actively metabolizing tissue. Thus if, instead of using living tissue, we make a homoiotransplantation of blood clots, in which active metabolism ceases presumably within a short time following transplantation, the

marked homoioreaction, which we observe, for instance, after transplantation of thyroid gland, is entirely or almost entirely lacking. Therefore, under these conditions, the blood clots behave, in general, as after autotransplantation. On the other hand, if we carry out a heterotransplantation of blood clots, definite differences appear, as evidenced by the greater activity of the connective tissue, the lymphocytes and polymorphonuclear leucocytes. Correspondingly, Siebert found that homoiotransplants, killed before transplantation by mild degrees of heat, no longer elicit a homoioreaction, while heterotransplanted tissue, under the same conditions, still calls forth a definite heteroreaction on the part of the host tissue. All these facts taken together suggest that homoiotoxins are either of metabolic origin, or, at least, are of so labile a character that they are destroyed when the protoplasm dies, whereas heterotoxins are preformed substances, comparable perhaps with endotoxins of bacteria, which can be extracted and which diffuse into neighboring tissue even from necrotic material. However, this delineation of the borderline between the homoiogenous and heterogenous action of tissues can at present be regarded only as a preliminary approximation; we do not yet wish to exclude the possibility that, under certain conditions, tissues which no longer metabolize actively may also give rise to homoioreactions.

If we then conclude that the reactions against homoiotransplanted tissues are due to the active metabolism of the homoiogenous tissues, or to the presence of very labile substances, the question arises, whether it might not be possible to alter the tissues before transplantation in such a way that they might still live and perhaps even regenerate, without however producing those substances which call forth the lymphocytic reaction. Experiments carried out, accordingly, in our laboratory by Siebert showed that it is indeed possible, through graded exposure of homoiogenous cartilage and perichondrium to moderate degrees of heat, previous to transplantation, to find an intensity of heat, which, while allowing the tissue to live and to regenerate, does not attract, to any extent, the lymphocytes of the host and that tissue exposed to this intensity of heat may thus be even better preserved than similar homoiotransplants not previously heated.

Autogenous substances as tissue regulators. We have learned that connective tissue, blood vessels and lymphocytes of the host behave in a different and, in each case, in a specific manner towards auto-, syngenesio-, homoio-, race or variety, and heterotransplants; the relationship between host and transplant determines in each case the mode of reac-

tion of the host against the transplant, and, in particular, the reaction between transplanted parenchyma and those tissues of the host which constitute the stroma or which take its place. In autotransplantation there is a marked development of capillary vessels growing into the graft from the surrounding host tissue. Fibroblasts of the host which likewise move into the transplant remain here relatively well preserved and do not tend to form much fibrillar material; instead, they may, under certain conditions, give rise to formations somewhat myxoid in character. It is very probable that the character of blood and also of lymph vessels secondarily influences the behavior of the fibroblasts and thus helps to determine the type of connective tissue which will develop; in so far the influence of the organismal differentials on the connective tissue would be an indirect one. How far in addition a direct regulation of the fibroblasts may take place, needs further analysis. Lymphocytes are not attracted by autogenous grafts. These facts indicate that the organismal differentials or substances, which carry organismal differentials as constituent parts, represent one of the factors which regulate the interaction of tissues, in particular the interaction between parenchyma and stroma. We may thus assume that substances of autogenous character regulate the behavior of blood vessels, connective tissue cells and lymphocytes. If these autogenous substances are replaced by others bearing a syngenesio-, homoio- or hetero-character, the relationships are changed. It is evident that the effect of these autogenous substances would be beneficial to the tissues and contribute to their nourishment. The organism would thus possess a system of very finely acting chemical autoregulators, which keep the vascular supply at a level adequate to the needs of the tissues and which prevent the fibroblasts from forming dense fibrous material, unsuitable for the nourishment of the functioning cells, and which furthermore provide for such an interaction of tissues as would ensure the normal tissue structure. These autoregulators, we must thus assume, carry the individuality differential of the organism, of which they are a part.

Tentatively we may suggest that these conceptions may perhaps help to explain, at least in part, the tissue changes which take place in old age. Here we find, in general, a decrease in active parenchyma and an increase in the formation of fibrous tissue in the stroma surrounding the parenchyma; the vascularization is diminished. Changes of exactly such a character might be expected to take place, if the production of the autogenous regulating substances on the part of parenchyma is diminished; in other words, if a decrease of specific metabolic substances, carry-

ing the autogenous differential, takes place in old age. We know, of course, that, in addition to such autogenous substances exerting a local action, and which we may therefore designate as contact substances, there are other substances acting from a distance, which regulate the interaction of tissues and which also undergo variations under different conditions.

Primary and secondary reactions. The question now arises as to the way in which the organismal differentials activate the tissues of the host, whether we have to deal with primary substances given off by the graft, or whether such substances act as antigens and call forth the production of secondary (immune) substances, which are responsible for the reactions. In the case of tumors we know that an active immunity can be experimentally produced. However, before discussing the active immunity in tumors and the bearing of this process on the interpretation of the mechanism through which organismal differentials produce their effect, we may state that, essentially, tumors possess the same organismal differentials as the normal tissues from which they originate, although there is some indication that possibly certain slight modifications in the individuality differentials may have taken place during the first development of tumors from normal tissues. In the large majority of cases, tumors show a difference in the reactions which they elicit after autotransplantation and after homoiotransplantation; the large majority of tumors can readily be autotransplanted, but they are sooner or later destroyed after homoiotransplantation, and this is true of malignant as well as of benign tumors. However, tumors differ from normal tissues in that they can be homoiotransplanted as well as autotransplanted in a certain number of cases; but even in such cases, the homoiotransplanted tumor differs in its mode of reaction from an autotransplanted tumor. The difference in the individuality differentials between host and transplant makes itself felt here also and the greater readiness with which certain tumors withstand the relatively unfavorable conditions prevailing in homoiotransplantation is, in part at least, due to the greater growth intensity, which distinguishes tumors from normal tissues, and which enables cancer cells to escape hostile reactions on the part of the host tissue, to which more sensitive normal tissues would succumb.

It has been shown by Ehrlich, Schoene, Bashford, Tyzzer and others that, through inoculation of pieces of non-growing tumor or of normal tissues, it is possible, in a certain number of individuals, to prevent the successful inoculation with another piece of tumor, which without the preceding immunizing inoculation, would have grown. Now, it is of

interest, from our point of view, that, if we wish to immunize against the growth of homoiogenous tumor, we must use for the first protective inoculation a tissue bearing the same species (homoio) differential as host and the homogenous tumor; if we wish to immunize against a heterogenous tumor, we must use, for the first inoculation, tissue bearing the species differential which is possessed by the heterogenous tumor, against which we intend to produce immunity. In this case the species differential used for immunization differs from that of the host.

We may, therefore, conclude that it is the organismal differential which is the agent that actively calls forth immunity. However, in the case of homoiotransplantation of tumors, it is only the homoiodifferential as such, or expressed differently, the introduction of the strange individuality differential, which sensitizes the host against the tumor subsequently transplanted. This tumor does not bear the same individuality differential, but merely the same species differential as the immunizing tissue and host. We have therefore to deal not with a specific immunization against a particular individuality differential in this case. We have reason to assume that this immunization by means of an organismal differential is only potent, in case there exists a primary difference between the individuality (strain) differentials of the host and of the tumor which is to be inoculated. The immune substances are therefore merely added to the primary homoiotoxins which would be active after inoculation of the tumor and the production of sensitizing immune substances presupposes the presence of primary homoiotoxins. The primary homoiotoxins, which are due to differences in the preformed individuality (strain) differentials of host and transplant, and the secondary, immune homoiotoxins, acting as sensitizers, call forth the same tissue reactions against homoiogenous tumor grafts as those which we described above in the case of homoiotransplantation of normal tissues. In both cases the vascular, lymphocytic and connective tissue reactions are modified in the same direction. It is Tyzzer and Burgess, DaFano and Murphy, in a series of varied experiments, who showed the importance of the lymphocytic reaction in tumor immunity.

In the case of embryonic tissues, the experiments of Fichera and Peyton Rous likewise have shown, that through a first inoculation of embryonic cells immune mechanisms are elicited which exert an inhibiting effect on embryonic tissues subsequently inoculated. We see then that in the case of tumors, as well as of embryonic tissues, the homoiodifferential of the transplant exerts not only a direct action—, that such a direct primary action does take place, is at least very probable—, but

that in addition it calls forth the production of secondary immune substances, which work in the same direction as the primary substances and intensify the effect of the latter. However, both tumor and embryonic cells differ, in certain respects, from ordinary tissues and it is therefore important that also in the case of normal erythrocytes it has been possible, through injection of these cells into individuals belonging to the same species, to produce hemolysins. Ehrlich and Morgenroth obtained this result in certain goats, and Todd succeeded in a similar way in cattle and sheep. The latter investigator immunized cattle with mixtures of the erythrocytes of a number of cattle. He thus observed that an immune serum was obtained, which hemolysed the different corpuscles used for immunization, but if such an immune serum was allowed to stand with the erythrocytes of one of the individuals whose blood was used for immunization, the antibody which was specific for the cells of this particular individual was absorbed by the erythrocytes and this hemolysin alone was removed from the mixture. This indicates that an individuality differential acted here as an antigen and elicited the production of an antibody, which was directed specifically against this differential. In this experiment the individualization of antigens and antibodies went therefore further than in the preceding instances.

We may then conclude that secondary or immune substances may play a rôle in homoiotransplantation.

In the case of transplantation of normal tissues, Schoene, influenced by his teacher Ehrlich, attributed lack of success of homoiotransplantation either to the formation of immune bodies or to athrepsia, which signifies withdrawal of food from the transplant by competing tissues. Schoene bases his conclusions on experiments in which he transplanted skin flaps from one animal into defects of skin in another animal. In case of homoiotransplantation in rabbits, he believed that a previous injection of liver, spleen or kidney tissue immunized the animal against a subsequent transplantation of skin; in mice, on the other hand, he did not succeed in demonstrating immune reactions. If we consider that many variable factors enter into the success or lack of success in skin grafting, and furthermore that in the large majority of cases a skin graft remains united with the host only temporarily, we realize that the definite proof of an active immunity will be beset with many difficulties. In the case of heterotransplantation,—grafting of mouse skin on rats,—Schoene apparently found more convincing evidence of active immunization.

We approached this problem by means of successive transplantations

of the same kind of tissue (thyroid and also other tissues) into the same host. If we had to deal with secondary (immune) reactions in the case of homoiotransplantation, it should be expected that the homoioreaction following a second transplantation, at a time when the homoioreaction against the first graft is already manifest, would appear much more promptly, because in this case the immune substances are already on hand, as a result of the first transplantation. The usual latent period following the grafting should be much abbreviated. However, in our experiments, there was no definite acceleration of the second reaction, against a homoiotransplant, noticeable. While our results do not permit us, as yet, to exclude entirely the coöperation of immune substances in the ordinary homoioreactions, they permit us at least to state, that the primary type of reaction is an essential factor in the fate of the homoiotransplant.

Our conclusions are also in agreement with the more recent experiments of other investigators, and especially of M. S. Fleisher, who found that previous immunization of an animal of the same species, by homoiogenous tissues, does not noticeably alter the kind and the course of reactions which develop around a homoiotransplant. In the case of heterotransplantation, Fleisher found that there is noticeable around the graft in an animal, immunized against tissues of that particular species, in the first few days following transplantation, an increased reaction on the part of the polymophonuclear leucocytes; furthermore, the ingrowth of fibroblasts into the transplant is somewhat delayed, under these conditions, on account of the more dense infiltration of the strange tissue by the leucocytes; in addition, the slight growth processes, which may take place for a short time in heterotransplants, are still further interfered with. But subsequently the reactions are here also the same, in the case of normal and of immunized animals. On the whole, there is more ground for assuming that secondary (immune) processes may participate in the reactions against heterotransplants than against homoiotransplants, because the heterodifferential would more effectively act as an antigen than the homoiodifferential; but also in the case of the former, the primary, direct reactions are evidently the essential factor. If we accept then the conclusion, that the reactions against strange organismal differentials are, in the main, primary reactions and if we further consider the fact, which we shall discuss later in this review, that the organismal differentials are dependent on and the expression of genetic factors, we can understand that it is not possible to alter basically the reaction of the host against the transplant, by repeated injections of the blood

serum of the donor into the host or vice versa, previous to or following transplantation. If Lexer noticed apparently a beneficial effect of such procedures, in case of syngenesiotransplantation, it can merely have been of a temporary character and not indicative of a real adaptation of the transplant to the host.

Another problem which we have to consider, concerns the question as to whether the organismal differentials act as such on the cells of the host, as simple toxins, or whether they assume their toxic character only after they have previously combined with a constituent of the body fluids of the host; in the latter case the homoio- and heterotoxins would have the character of complex substances. The former assumption seems to be sufficient at the present time to explain the experimental findings; however, the second interpretation must still be considered as a possibility.

As to the mode in which the homoiotoxins, given off by a transplanted piece of tissue, act on the host cells, an experiment carried out by Crossen is instructive. He showed that from an autotransplanted lymph gland, lymphocytes are attracted towards a piece of homoiotransplanted cartilage placed in close approximation to the lymph gland, but not towards a similarly placed piece of autogenous cartilage. Apparently the lymphocytes are mobilized by the strange individuality differential, diffusing in the direction towards them, and they respond to it by increased amoeboid movements, oriented towards the homoiotransplant.

We may then conclude that the organismal differentials, as such, act as toxins in strange hosts, affecting the cells of the latter, and we may furthermore conclude that the homoiotoxins are produced essentially by actively metabolizing cells, while heterotoxins may also be given off by necrotic tissues.

Modifications in the reactions of the host against transplants. Under certain conditions it is possible to produce changes in the reactions of the host tissue against a transplant, or to modify in vitro the action of the body fluids of an individual towards a piece of strange tissue.

Thus, I observed that, after homoiotransplantation of cartilage, not only no cumulative effect, in the reaction of the host against the transplant, takes place, with the increase of time during which the transplant is kept in a host, possessing an individual differential which differs from that of the transplanted cartilage, but, on the contrary, in the course of time a diminution in the number of lymphocytes may be found around the graft. It appears as if, somehow, a gradual adaptation

occurred between the transplanted tissue and the host, but on what conditions this adaptation depends or wherein it consists, is not yet certain.

While in this case we have to deal with a spontaneous adaptation between host and transplant, in the experiments of Rhoda Erdmann and Gassul it was brought about experimentally. The former had observed that through previous cultivation in vitro, embryonic bird tissue can be made to remain alive for a longer time after subsequent homoiotransplantation into adult birds. Both these authors found, similarly, that in amphibia, skin from an adult animal, which had previously been cultivated in vitro lives, after transplantation into a heterogenous host, for a longer period of time, than the same kind of skin heterotransplanted without previous cultivation in vitro. According to Rhoda Erdmann it is necessary to adapt, in vitro, step by step, the skin to the heterogenous body fluids, before its transplantation into the living animal, and the time necessary for preliminary cultivation in vitro is a measure of the difference in organismal differentials between host and transplant.

Also Kimura found, however apparently only in one experiment, that, by cultivating for a longer period of time bird fibroblasts in vitro, in heterogenous plasma with the addition of heterogenous tissue extract, these cells assumed the antigenic properties of the species, in the plasma of which they had been cultivated, as revealed subsequently by the precipitin test. It seems that there may remain, perhaps, in this experiment the possibility that, with the tissue, a small quantity of the heterogenous plasma was injected into the animal which was used for immunization, and that this admixture might have been responsible for the result of the precipitin test.

Somewhat similar is the result obtained by Lumsden, who found that when a mouse tumor has been transplanted into a rat and has temporarily grown in this heterogenous host, and when subsequently cells from such a mouse tumor are grown in vitro in rat serum, these cells were no longer cytolysed in vitro by the heterogenous serum, as would have been the case with cells from the same mouse tumor, if it had previously been transplanted into a mouse and grown here instead of in a rat. However, that no real change in the organismal differential had taken place in the cells of the mouse tumor, as a result of this temporary growth in the rat, is evident from the fact that, after retransplantation into the rat, these mouse tumor cells behaved exactly like mouse cells and not like rat cells: bearing a heterodifferential, they perished here within a very short time. The same result was obtained with rat tumor cells, which

had grown temporarily in a mouse. It might be suggested, as a possibility, that in these experiments the body fluids of the host somehow combined with the transplanted heterogenous cells and thus exerted temporarily a protective effect on these cells in vitro.

However, that no real change in the original differential of these cells had taken place, follows also from recent experiments of A. Fischer, who found that rat fibroblasts, that had grown previously for a period of two and one-half years in chicken plasma, showed the same sensitiveness towards immune cytotoxin produced against rat tissue as did normal rat tissue. The rat cells had therefore retained their own species differential, notwithstanding their long continued growth in chicken plasma.

Still, it is perfectly conceivable that through certain chemical or physical alterations of a tissue, previous to transplantation, not only the reaction of the host against a strange organismal differential may be changed, but that the organismal differential may undergo a certain modification. It is, for instance, conceivable that the amount of differential, produced by a tissue thus treated and diffusing into the surrounding host tissue, might be diminished. This seems to be the case in the experiment of Siebert, to which we have already referred in another connection. Siebert showed that, by exposing a piece of cartilage in vitro to a graded intensity of heat, and subsequently using it for homoiotransplantation, the lymphocytic reaction could be much diminished, while at the same time the heated tissues remained alive and were able to undergo regenerative growth.

The character of the reaction against a strange differential can be modified according to the site of transplantation. The most striking instance of this kind is transplantation into the brain. Shirai first showed that heterogenous tumors, which would not grow elsewhere, might grow when transplanted into the brain. Murphy confirmed this fact and found moreover that, after such transplantation, the usual lymphocytic reaction is lacking, but can be elicited again, if, simultaneously with the grafting of tumor cells into the brain, a piece of spleen is transplanted. The spleen thus restores the power of the organism to react against the heterodifferential of the tumor in a place where otherwise the reaction would have been lacking. This observation applies to transplantation of heterogenous tumors. In the case of transplantation of homoiogenous tumor into the brain, this organ seems to behave similarly to other tissues, according to E. Harde.

It was of interest to compare with the behavior of tumor tissue, that of normal tissue possessing a well characterized individuality differential,

and likewise transplanted into the brain. In such experiments Siebert showed that, also after homoiotransplantation of thyroid gland into the brain of guinea pigs, the lymphocytic reaction is much diminished around the transplant and that under these conditions the transplant remains longer preserved than after homoiotransplantation into the subcutaneous tissue; but notwithstanding the diminution in lymphocytic reaction, a homoiotransplant in the brain differs from an autotransplant, in the very marked connective tissue reaction, which the former elicited here, and in the diminution in the amount of preserved homoiogenous tissue; besides, the lymphocytic reaction was merely weakened, but not abolished. What the factors are, on which this distinctive characteristic of the brain depends, is not yet known. It is possible that the organismal differentials are less well developed, although not altogether lacking, in the brain; the latter would, then, in this respect behave like the lens, an assumption for which indeed some evidence exists. It is also possible that the "barrière haemato-encephalique" (L. Stern) inhibits the passage into the brain of certain substances or cells which play a part in the reaction against strange organismal differentials.

In some ways transplantation in embryonic structures bears some similarity to transplantation into the brain. Thus the experiments of Murphy and others have shown that certain heterogenous tumors, and perhaps also heterogenous embryonic tissue, can be successfully transplanted to the chick allantois and here remain alive without eliciting a heteroreaction; it may even for some time be transplanted from chick to chick and thus be kept alive for a longer period of time. However, the transplant grows on the allantois only until that stage in embryonic development has been reached, when the mechanism, which makes possible the reaction against the strange differential, can manifest itself, and it may be added that there is some indication that the reaction in the embryo depends upon the full activity of the reticulo-endothelial tissue. We may then conclude that the mechanism, on which the reaction against strange organismal differentials depends, originates only at a certain stage in embryonic development and that emdryonic cells, as such, are not necessarily endowed with the property of reacting against these differentials. Even in newly born animals the reaction may be less pronounced than in adult animals. Thus our observations, as well as those of Tureen, showed that in guinea pigs, serving as hosts within the first ten days of life, the connective tissue and lymphocytic reactions, which take place against homoiotransplanted thyroid gland, are distinctly diminished, as compared with the reactions in adult guinea

pigs, and the transplant is therefore, on the average, better preserved in very young than in old animals. Only secondarily the lymphocytic reaction may become very strong in young animals, and even stronger than in adult hosts, because, on account of the diminished intensity in young animals of the connective tissue reaction, which normally appears in adults at an early date following transplantation and which exerts a very unfavorable effect on the transplant, the lymphocytes have subsequently a better chance to accumulate and to exert their destructive function in young animals. A homoiotransplantation in a young host, thus, is not unlike a syngenesiotransplantation in an adult animal.

These observations are in harmony with certain other experiences, in particular with the late appearance, at the end of embryonic life or soon after birth, of the serum-agglutinins in man, which cause the agglutination of erythrocytes belonging to a different blood group. They agree also with the well known fact that the production of immune bodies does take place less readily in very young than in older animals (Famulener). Furthermore, it is known that, in general, cells of very young animals are less sensitive to the action of certain toxic substances and that they react less actively against them than cells of older animals.

Time of development of organismal differentials. However, there is reason for believing that it is not only the mechanisms, on which the reactions against organismal differentials depend, which are not preformed, but are only potentially present in the germ cells, but that this is true also of the organismal differentials themselves. The reaction mechanisms, according to this view, are produced only at a rather late phase of embryonic development; the organismal differentials, which under certain conditions may function as antigens, form apparently at an earlier date.

In this connection we may refer to the experiments of Braus, who showed that, through injection of larvae of amphibia into rabbits, precipitins cannot be produced, whereas injection of adult material is successful; presumably the larvae contain as yet no precipitinogenic antigen. On the other hand, Roessle found that mammalian and avian embryos do contain antigen which is able to produce hemolysins. It is further of interest that the human blood group antigens, on which the presence of the so-called isoagglutination depends, seem to develop in the erythrocytes and other tissues only in the course of embryonal life, although they are potentially present in the germ cells.

There is thus some reason for assuming by analogy that also the organismal differentials are produced only at certain stages in embryonic

development. However, it is not probable that the different kinds of differentials are formed all at the same stage of embryonic development; but, on the contrary, it is more likely that the more primitive and basic differentials, like the class and generic differentials, develop before the species differentials, and that the latter develop before the individuality differentials, which correspond to the finest, most delicate differentiation.

In harmony with this conception are, also, the facts established, in transplantation of organisms or of parts of organisms, representing more primitive ontogenetic and phylogenetic stages. A very large number of experiments by many investigators, among whom may be named Born, Wetzel, Korschelt, Harrison, Lewis, Spemann, Goetsch and Rand, and to which only a brief reference can be made in this review, have shown that, in general, transplantability increases with the ontogenetic and phylogenetic primitiveness of the organisms which serve as hosts and donors. The great range of differentials, which by means of transplantation may be joined under those conditions, without the manifestation of reactions indicative of serious incompatibility, may result from the lack of power on the part of the host to react against the graft, or to a lack of sensitiveness of the transplant; but it may, in addition, be due to the lack of a full development of the differentials, as such, in very primitive organisms; these various possibilities have so far not yet been separated in theoretical discussions. Furthermore it will be necessary, in evaluating these data, to consider the fact that in the majority of the experiments in lower forms, in plants as well as in animals, we have not to deal with transplantation in the restricted sense, in which we apply this term in experiments in higher organisms, but with a mode of procedure corresponding more closely to what in the latter is designated as parabiosis, which we shall discuss later in this review, inasmuch as not only the host is able to carry on an independent life, but also the graft. However, it is quite possible that, also in primitive organisms, individuality differentials, as well as the mechanism of reacting against strange individuality differentials, develop; thus, in certain protozoa, we find such reactions very fully developed, as the experiments of Schultze, Jensen and others have shown.

The genetic basis of organismal differentials. The relatively fixed character of the organismal differentials and of the mode of reaction of organisms against strange differentials is understandable, if we trace the origin of these differentials and of the reactions against them back to the fertilized ovum, and show that they are genetically determined. The conclusion, that the organismal differentials are due to the genetic

constitution of the organisms, is based on the correspondence between the character of the differentials and the relative intensity of the reactions against strange differentials, on the one hand, and the genetic relationship of the organisms, which are the bearers of the differentials, on the other hand. This holds good if we consider the animal and plant system as a whole; but, as we have seen, in a general manner it holds good also, if we investigate the individuality differentials within the same family. They are on the average more nearly related to each other, as revealed by transplantation, than the individuality differentials of non-related organisms within the same species and strain. Moreover, under these conditions, we do not find abrupt differences in individuality differentials, but all kinds of transitions. Thus, if we transplant tissues from brother to brother within the same family, we observe, in addition to the typical intermediate syngenesio-effects, reactions approaching, on the one side, those characteristic of autotransplantation and, on the other side, those of homoioreactions On the whole, transplantations from brother to brother give the best results. As to the transplantations from children to parents or from parents to children, they are usually not quite so favorable as those from brother to brother. Transplantations from grandparents to grandchildren and vice versa behave similarly to the exchange of tissues between parents and children. The existence of a continuous series of intergrades suggests that multiple factors determine the character of the individuality differentials and therefore also the fate of the transplants.

As to the method used by us in the analysis of organismal differentials, it renders possible the recognition of the finest gradations in differences of individuality differentials and, indirectly, also of the recognition of the differentials as such. Thus a whole series of gradations is found in transplanting tissues into strange hosts. It is true the method used by us and our associates is laborious and time-consuming, but it alone makes possible the recognition of finely graded differences in organismal differentials. If we merely determine, as is so often done in investigations in transplantation, whether a transplant takes or does not take, these fine gradations cannot be recognized.

The most probable assumption is, that the individuality differential depends upon the totality of genes present in host and donor, and upon the relation of these two sets of genes to each other. Furthermore, it is very probable, that it is the strange genes present in the donor that are provocative of the reaction; it seems that the greater the number of strange genes in the donor, and the greater the strangeness of the genes,

the more severe will be the reactions on the part of the host against the transplant. However, there is some ground for assuming that the Y chromosomes may possibly not be concerned in these reactions, because it does not seem that it makes any difference, whether host and donor are of the same or of different sex. But even the Y chromosomes may possibly come into play in certain instances; at least in the case of transplantation of certain tumors. Strong recorded some experiments in which the sex of hybrids seemed to affect the result. It is also of interest to note that if the relation between donor and host is reversed, the results of transplantation, as manifested in the intensity of the reaction against the transplant, do not need to be identical; no simple reciprocity therefore exists. This can be readily understood, if we consider that it is the host which reacts against the transplant and not the transplant which reacts against the host, or at least that, under ordinary circumstances, we have no means of determining the reaction on the part of the transplant against the host. This fact again can best be explained by the assumption that it is the presence of strange genes in the transplant which calls forth the reaction in the host. The correctness of these views was further tested by us in transplantations which we carried out in families of inbred animals.

The effect of close inbreeding on individuality differentials. I. *In guinea pigs.* It was of great interest to determine the changes which would take place in the character of the individuality differentials as a result of close inbreeding. Thanks to the coöperation of Dr. Sewall Wright, who supplied us with five inbred families of guinea pigs, and of Dr. Helen D. King, who placed at our disposal her strains of inbred rats, we were able, with the aid of these investigators, to carry out the same kind of transplantations which we had previously carried out in non-inbred animals. The guinea pigs had been inbred for more than twenty generations, through successive brother and sister matings, and the rats had been similarly inbred through more than forty generations.

As far as the experiments with guinea pigs are concerned, we found that, within an inbred family, the individuality differentials between apparently distant members of such a family had become much more similar to each other than are, on the average, the differentials between brothers in non-inbred families. The similarity might become so great between two individuals of the same inbred family, that, in some cases, for a number of months, the reaction of the host against the transplant resembled an autoreaction, and only after as long a period as five months, following transplantation, did the still existing slight difference between

the individuality differentials of two individuals, which were not brothers, make itself felt and lead, at this late date, to the development of a lymphocytic reaction, which injured the transplant. Associated with such a lymphocytic reaction, was a secondary slight proliferation of connective tissue. Such a reaction proves that, while an autogenous state had been approached, it had not yet been completely reached under those conditions; it seemed that, especially in the members of certain inbred families, the identity of individuality differentials had been approximated more closely than in others. As a further proof of the great similarity between differentials attained in these families, we may mention that successive transplantations of the same piece of thyroid gland from one host to another could be successfully carried out. Under these conditions, we observed also mitotic proliferation of liver cells in pieces transplanted into other individuals, a result which we have so far not obtained in non-inbred families. Furthermore, it is possible in inbred families to transplant successfully as many as four lobes of thyroid gland, from one individual into another one, possessing its own thyroid gland, and thus to prove that a deficiency in thyroid hormone is not required for the successful transplantation of this organ with internal reaction as had been assumed, among others, by Halsted. Also transplantations of such organs as bone marrow and ovary may give excellent results under these conditions. In case of brother to brother transplantations, within inbred families, the resemblance to autotransplantation is still closer; but even here, in certain strains, slight discrepancies in the composition of the individuality differentials may still be demonstrated by means of the lymphocytic reaction. There was some indication that the results of transplantation were not quite so favorable if, instead of exchanging tissues between brothers belonging to the same inbred strain, we exchanged tissues between two brothers which were hybrids between two different inbred strains. Thus, experiments of this type in inbred families, will allow a very fine analysis of the individuality differentials. In general, the results of transplantations within an inbred family were the better, the greater the number of generations through which inbreeding had been practiced, and there was also some indication that if, within the same family, two subfamilies developed, between which no interbreeding had occurred for a number of generations, the result of exchange of tissues between such subfamilies was not so good as the exchange of tissues between more closely related members of the same family. In control experiments, in which tissues were transplanted from one inbred family to another, in general, homoioreactions were obtained, in accordance with expectations.

Of great interest were the results which we obtained, when we transplanted tissue from a hybrid between two inbred families to one or the other of the two families which had been used for hybridization, or vice versa. Transplantation from component strains to hybrid gave results similar to those observed after transplantation within the same inbred family. The grafts were well preserved under these conditions, the preservation being much better than after transplantation from brother to brother in non-inbred families, although not as good as after autotransplantation. On the other hand, transplantation from hybrid to one of the component families was much more unfavorable; still the result, even in this case, was much better than that of ordinary homoiotransplantation, being much like that obtained in syngenesiotransplantation, in case a relatively marked difference in the composition of the individuality differentials, between host and donor, existed. These results were thus in agreement with the interpretation of the interaction between individuality differentials, which we have given previously. As stated above, we assume that the host reacts against the strange constituents in the individuality differentials in the donor, while on the other hand, constituents in the individuality differentials of the host, which are not represented in the donor, are of much less importance. However, we cannot yet exclude, with certainty, the possibility that the lack of some constituents in the individuality differentials of the donor, which are present in the host, is of no influence whatever, as far as the reaction of the host against the transplant is concerned. Such a result of the experiments could not have been foreseen with certainty. On the contrary, it was conceivable that it is the greater number of differences, between the differentials of host and transplant, which is the deciding factor, and that it is of no importance whether it is the host or the donor differentials which have certain characteristic features. If we assume that, in proportion to the greatness of the difference between the differentials in host and donor, a toxic substance develops which determines the reaction, then our findings would be difficult to explain; but if, on the other hand, we assume that the genes of the donor which are strange to the host, determine the development of abnormal substances, then results, such as we obtained, should be expected.

Our conception is also in accord with experiments of Little, in which he transplanted spleen from hybrids between Japanese waltzing and white mice to one of the parent strains, and from one of the parent strains to hybrids. The results of the latter kind of transplantation were identical with the results of autotransplantation, while the former type of

transplantations resulted in homoioreactions. The method used by Little in these experiments did not, however, make possible the discovery of graded differences in the constitution of the individuality differentials, in the tissue used for transplantation, and we may therefore consider it as probable that also in Little's experiments there resulted, as in ours, various types of intermediate reactions. In this connection it may be remarked that it seems precarious, on the basis of the determination of the number of "takes" of a tumor, or of a normal tissue, to determine the number of genetic factors which are required for the growth of the tumor or tissue, because, as stated above, the determination of "takes" does not furnish a clear picture of the real complex of conditions underlying the growth; in other words, it does not reveal the character of the individuality differentials. Furthermore, our conclusions can be harmonized with earlier experiments by Tyzzer and Little and by Fleisher and myself, in which we transplanted tumors into successive generations of hybrids between different strains of mice. Transplantation of a tumor into the first generation of hybrids gave results similar to those obtained after transplantation into the original strain. However, in our experiments, we did not have to deal with individuality differentials, but with strain differentials, and Tyzzer and Little, in their experiments, approached species differentials. The tumors which were used in those investigations grew very well after homoiotransplantation into the same strain and were thus not suited for the analysis of such fine differences as are characteristic of individuality differentials. Little and Tyzzer interpreted their results, in the manner in which the hereditary transmission of a certain character is explained; for instance, the transmission of one or the other color from the parents to the F 1 and F 2 hybrid generations; this depends upon the dominance or recessiveness of the genes representing these colors, and the presence of certain genes is necessary for the transmission of the corresponding character. Accordingly, the growth of tumors in F 1 generation was explained by these authors as indicating that a single dose of genes was sufficient to insure the growth of the tumor; whereas according to our interpretation the reaction depends upon the presence or absence of strange genes or their derivatives in the transplant.

If, instead of using, for the analysis of the individuality differential, transplantation in hybrids between inbred families, we carry out syngenesiotransplantation in families obtained through the usual random mating, we should expect, in accordance with the results obtained in inbred families, that transplantation from parent to child would give

better results than the reciprocal transplantation. We found this to be so in some cases; but, in other cases, we did not obtain concordant results, nor did Schoene in his series of syngenesiotransplantations. The variability in the outcome observed, under these conditions, may be due to several factors. In the first place, the variations in the genetic constitution of the germ cells are much greater, in random matings, than in matings between inbred families, and correspondingly the individuality differentials of brothers and sisters from the same mating may differ considerably. Furthermore, in different matings, father and mother vary as regards the similarity or difference of their individuality differentials; in addition, secondary factors, as for instance, the age of the host may vary in different transplantations. Thus, it happened that, in those experiments in which we transplanted pieces from parent to child, father and mother belonged to different varieties, in a greater number of cases, than in the reciprocal type of transplantation, and this factor was apparently sufficient to turn the scales slightly in favor of transplantation from child to parent in this series. The variable results obtained in case of random mating can therefore be readily understood and they do not invalidate the consistent results obtained in experiments with inbred families.

II. *Inbreeding in rats.* If we compare with the changes in individuality differentials, which take place in guinea pigs as the result of inbreeding, the changes which occur in inbred rats, we find here, likewise, that the individuality differentials become somewhat more similar in different animals belonging to the same inbred strain, but it is interesting to observe that the increase in similarity between the differentials in the rat was much smaller than it was in the case of the guinea pig, notwithstanding the fact that in the rat the number of generations, inbred by means of brother and sister matings, was much greater than in the guinea pig, the former having been inbred, at the time of our first experiments, through as many as 40–45 generations. In more recent experiments, we were able to use rats, inbred through more than 60 generations, and although it seems that some progress has been made in the increase in similarity between the different individuality differentials, still even now the level attained by the inbred guinea pigs has apparently not yet been attained. However, the last named investigations are not quite completed and we must therefore, at present, make some reservation as to our ultimate conclusions.

If we inquire into the causes for these differences in inbred rats and guinea pigs, we have to consider three possibilities: (1) In the case of

the rat, Doctor King practiced selective mating, in every instance the most vigorous individuals in a litter being chosen. Thus, the inbred rats remained on the whole healthy and fertile, while in the inbred guinea pigs, in which such a selection did not take place, a definite decrease in strength and fertility seemed to have occurred. There is reason for assuming that the most vigorous rats were usually those in which the individuality differential remained most "individualized," and which had least attained the average constitution. (2) In the case of transplantation in rats, individuals were used, more often than in the case of guinea pigs, that belonged to subfamilies which had branched off from other subfamilies a considerable number of generations before. Gradually the dissimilarities existing between the different subfamilies were thus accentuated. There were two strains, A and B, of inbred rats, which had been bred separately by Doctor King, although originally they were derived from the same stock. The individuality differentials of rats of strain A had become about as distinct from the differentials of those of strain B as the differentials of ordinary non-related rats; they had the character of homoiodifferentials. However, after many generations of inbreeding, within each of these two strains, one would have expected that, within strain A and within strain B, the individuality differentials had become so similar in the animals belonging to these strains, that the separate breeding of subfamilies would not have led to the development of combinations of genes which were as distinct from each other as ordinary homoiodifferentials. (3) The possibility has to be considered that mutations occur, in the inbred strains, creating genetic dissimilarities. If this does take place, it would, of course, explain the persistence of differences in individuality differentials in inbred stock.

As in the case of transplantations in non-inbred families, so also in inbred families, we find that, if multiple transplantations of different types of tissues are made simultaneously, the same host being used, the relative intensities of the reactions depend on the relation of the individuality differentials of each donor to the host.

Genetic constitution of organismal differentials. These investigations in inbred animals confirm then the conclusion, that the differences in the individuality differentials depend upon the differences in the genes of two individuals; at the same time, for the reasons stated above, we may assume that it is not the genes, as such, which are the real units composing the differentials, but that they are the precursors of the units, the differentials consisting of gene derivatives. These differentials are the same in the large majority of all the cells of the same organism and in-

asmuch as it is the chromosomes which are identical in the constituent tissues and cells of an organism, while the cytoplasm differs, it seems most probable that it is the chromosomes, or rather the genes of which they are constituted, which ultimately determine the character of the organismal differentials. However, considering the fact that non-nucleated erythrocytes also possess the species differentials and probably even the individuality differentials, we cannot locate these differentials as such in the chromosomes, but can merely attribute to the chromosomal genes the function of interacting in such a way with certain constituents of the cytoplasm, that here those gene derivatives develop which constitute the organismal differentials.

Furthermore, we may conclude that the organismal differentials are not represented by a single unitary substance, characteristic of each organism, but that they consist of discrete units, the gene derivatives. This follows from the experiments in inbred families and agrees also with the views of Correns. It seems probable that all the genes are of significance as determiners of the organismal differentials, with the possible exception of those contained in the sex chromosomes, and this conclusion would harmonize with the finding of many reaction grades in transplantation, suggesting that the number of the determining units must be large. It is furthermore probable that these gene derivatives, which constitute the individuality differential, after transplantation of a tissue, act as such on the host, with or without previous interaction with constituents of the body fluids of the latter.

The homoiodifferentials are, as far as we know at the present time, active only in living metabolizing cells, while the heterodifferentials are active also in dying or dead cells, provided the tissues have not been previously subjected to severe chemical alterations.

These differentials are also responsible for the activation of certain special mechanisms, which determine the mode of reaction on the part of the host towards the transplant, carrying the strange differential; they cause the mobilization of connective tissue cells, lymphocytes, blood vessels and perhaps the reticulo-endothelial cells. These elements are quick to respond to differences in organismal differentials. Furthermore, there is reason for assuming that it is these organismal differentials which represent primarily the antigens of an organism, although of course, in addition, other substances may function as antigens. Superimposed upon these organismal differentials, organ or tissue differentials may likewise act as antigens. Thus we may summarize tentatively our conclusions concerning the constitution and function of the organismal differentials.

Genetic composition in transplantation and fertilization. It was O. Hertwig who seems first to have recognized the similarity between fertilization and transplantation; he expessed the opinion that these two processes take a parallel course. W. Schultz attempted then to demonstrate this parallelism in experiments, in which he compared exchange of tissues between hybridizable and non-hybridizable animals, and also between animals furnishing tokonoth and steironoth hybrids. Poll designated as tokonoth hybrids, those which are fertile, while the steironoth hybrids are sterile. Schultz concluded that exchange of tissues between animals furnishing tokonoth hybrids succeeds better than exchange between animals in which the hybrids are sterile. However, it must be stated that the experiments on which Schultz based his conclusions were not always sufficiently numerous to make his conclusions secure.

In a general way, it is true that there exists a parallelism between the results of transplantation and fertilization; but the parallelism is not complete. Thus the optimum for transplantation is found, when individuality differentials are identical in host and donor, while in fertilization a homoiogenous relation between male (donor) and female (host) is the usual one and leads to normal results. In some cases of hermaphroditism in animals and plants autofertilization is impossible, while homoiofertilization succeeds. Hertwig was not yet aware of these differences between transplantation and fertilization, because the differences between auto- and homoiotransplantations had not yet been fully recognized at the time when he advanced his theory. We now can foresee that differences should exist between fertilization and transplantation, as far as organismal differentials are concerned. In fertilization, the spermatozoön containing its set of genes is placed into a new environment, where it must interact with the nuclear genes and the cytoplasmic substances of the egg. In transplantation the organismal differentials of the transplant interact with those of the host. The differentials are, as far as we know, not identical with genes, but are probably, as we have explained above, gene derivatives. Moreover, in the case of transplantation special mechanisms of reaction on the part of the somatic host tissue against the somatic transplant have developed in the higher organisms, while in fertilization incompatibility between chromosomes of sperm and chromosomes and cytoplasm of ovum lead to disturbances in development and to faulty interaction between the chromosomes of sperm and ovum. This explains the fact that, while in general incompatibilities in fertilization as well as in

transplantation are the more marked, the farther distant the interacting species are, a perfect parallelism between these two processes does not exist. The correspondence between fertilization and transplantation as far as it exists, depends upon the fact that in both processes the result is determined by the genetic composition, and as far as there exist differences, they are due to the fact that the rôle played by the genes in these two processes is not identical.

Individuality, transplantation and potential immortality of somatic cells. About 30 years ago the writer, and soon afterwards Jensen, showed that it is possible to transplant tumors through many consecutive generations of animals; there was apparently no inherent limit to such propagation of tumor cells, inasmuch as the termination of such a series depended merely on avoidable accidental factors. It was evident that tumor cells are only ordinary tissue cells which secondarily become transformed into tumor cells, under a variety of more or less well defined conditions. On the basis of these data, I drew the conclusion that tumor cells, as well as the tissue cells from which they were derived, have the potentiality of immortal life. But while it was possible to transplant the rapidly proliferating tumor cells apparently indefinitely, the serial transplantation of ordinary tissue cells succeeded only to a very limited extent; in the main this result was due to the differences in the individuality differentials in host and transplant. Epidermis could thus be transplanted serially for only a relatively short period. However, in the case of cartilage, which apparently gives off homoiotoxins to a less extent, which is more resistant and seems to become adapted to the host after a certain time, serial transplantation succeeded much better and we thus could keep cartilage alive for a much longer period than the usual duration of life of the animal, of which the cartilage had formed a part. In this case, the connective tissue was the principal agent, which caused the injury and destruction of the transplanted tissue, and not the lymphocytes. While under normal conditions, when autogenous substances are active and the tissues are sufficiently supplied with oxygen and other necessary food material, the neighboring connective tissue remains at rest, presumably under the influence of the autogenous regulators, given off by the metabolizing cells, under conditions prevailing in serial homoiotransplantation, metabolic processes in the transplanted tissue become unfavorable, and thus processes of differentiation and the formation of paraplastic substances take place; gradually, if a cumulative action of unfavorable conditions occurs, necrosis of the transplant or of parts of

it occurs. Under these circumstances the restraining effect of the grafted tissue on the surrounding host tissues is diminished or lost, and connective tissue, no longer being held in check, invades the transplant. It is of interest to know that, if unfavorable factors are active after autotransplantation,—as they sometimes are,—it is mainly the host connective tissue, rather than the lymphocytes, which attack the transplant. However, after autotransplantation, after some time regulative mechanisms set in, which are much less prone to become active, when homoiotoxins exert their unfavorable influences on the graft. As a result of these added injuries gradually larger and larger parts of the transplant become invaded and destroyed, mainly by connective tissue. Therefore, in the end the transplanted cartilage, propagated from rat to rat for several years, dies and the experiment is thus terminated. It is different in tissue culture, where the aggressive action of host tissues is eliminated and where, according to Carrel and Ebeling, fibroblasts can be propagated serially, apparently indefinitely.

Transplantation of skin, in general, and the behavior of pigmented skin, in particular, in the analysis of organismal differentials. We have so far discussed the transplantation of tissues and organs into pockets of the subcutaneous tissue (heterotopic transplantation). In the case of skin, however, the grafting is usually done on superficial defects in the skin itself (isotopic transplantation). Skin transplanted in this way offers some peculiar problems and, at the same time, it makes possible, if we take advantage of differences in pigmentation in the skin of host and donor, a still deeper analysis of organismal differentials. On the other hand, this method of transplantation has also some serious disadvantages. Skin grafting done for practical purposes by the surgeon is always carried out in that way. Now, under those conditions, it is often difficult to determine accurately the fate of the transplant. Therefore, in the past, many surgeons believed that skin could readily not only be autotransplanted but also homoiotransplanted. It is especially through the work of Lexer and Schoene that this view has been shown to be erroneous. Homoiotransplantation of the skin does not succeed as a rule, while autotransplantation usually does succeed. There is still some difference of opinion as to whether syngenesiotransplantation may or may not succeed. Lexer denies it; others, like Schoene, believe that it may succeed in some cases. Our own investigations and those of our associates also make it probable, on theoretical as well as on experimental grounds, that syngenesiotransplantation may succeed under especially favorable circumstances.

Blood groups and transplantation of skin. There is another problem of theoretical significance in transplantation of skin; it concerns the significance of blood groups. It has been maintained by a number of surgeons, that the result of homoiografting of skin largely depends upon whether donor and host do or do not belong to the same blood group. At the present time, the vast preponderance of opinion rejects such a connection; it is again mainly Lexer and his associates, as well as Holman, whose experience has disproven such an assumption. In accordance with the theoretical considerations developed by us, it appears, a priori, as very improbable that the blood group of donor and host can be of great significance in this connection. The individuality differential is determined by all or at least by a large number of the genes of an individual, while the blood groups depend upon a few genes only. At best, these genes, being presumably constituents of the gene-set characteristic of the differential, may contribute in a small way to the result of transplantation, but cannot be a decisive factor. These particular genes can determine the fate of homoiotransplants as little as identity of heterophile antigens, among different classes of animals, makes heterotransplantation between these classes possible.

Blood groups, organismal differentials and constitution. In this connection, it might be appropriate to refer to the view, only recently expressed by Krischewski, that it is the blood group to which an individual belongs which determines his constitution. This view cannot be correct, for the same reason that transplantation of skin is not determined by the blood groups. The constitution of an individual, that is, his mode of reaction, as far as it is determined by genetic factors, depends primarily upon his organismal differentials and, in particular, upon his individuality differential and secondarily upon his tissue and organ differentials.

Transplantation of pigmented skin and organismal differentials. As far as the transplantation of pigmented or unpigmented skin into defects of skin, which differ in pigmentation from the graft, is concerned, it has been possible by means of this kind of transplantation to discover effects of organismal differentials, which heterotopic transplantation, to which we have mainly referred in our previous discussions, did not reveal to us. In particular, do such experiments give us an insight into the mutual equilibrization and desequilibrization of tissues, which apparently also depend upon the action of contact substances, but which manifest themselves in specific ways, in addition to the usual reactions on the part of lymphocytes, connective tissue and blood vessels. However, the

substances which determine such reactions may be not only organismal differentials, but also tissue differentials. Thus the action of the latter was observed by us after autotransplantation of black and white skin, into defects of white and black skin respectively, in the guinea pig. In this case the pigmented host skin invades the transplanted white skin, or in case pigmented skin has been used for grafting, the latter invades the adjoining white skin of the host. However, it is difficult in this condition to decide with certainty whether we have to deal merely with an invasion by epithelial chromatophores or with an invasive growth of the whole epidermis, although the latter assumption appears much more probable. Also Carnot and Deflandre observed these phenomena, but they assumed erroneously that homoiotransplanted and, under certain conditions, even heterotransplanted skin may heal on, and it would then be impossible to know whether to attribute the effects observed to organismal or to tissue differentials. Sale and Seelig have shown that homoiotransplantation of pigmented or unpigmented skin does not succeed as a rule. In a few cases in which black skin, tranplanted into defects of white skin, healed in in different individuals, we had presumably not to deal with homoiotransplantation, but with syngenesiotransplantation. Under these circumstances, the difference in individuality differentials between host and transplant prevented the grafted epidermis from invading the white host epidermis; instead, the transplant suffered as a result of toxic conditions in the strange host and the grafted cells were unable to produce pigment in the normal manner.

Subsequently comparative studies of this kind were made in various classes of vertebrates, and an analysis of these investigations shows that a thorough microscopical examination of successive stages in transplantation is necessary for the correct interpretation of such experiments. Only, by these means, effects of differences in organismal differentials are discovered, which otherwise would escape recognition. Especially valuable in this connection are the experiments of Cole, Hadley, May, Kolodzierski, Taube and Weigl. We must limit ourselves to a statement of the principal conclusions to be drawn from the investigations of these authors.

If we compare the results of transplantation obtained in this whole series, we observe, in a general way, that the higher the systematic position of the species concerned, the finer are the reactions which take place in response to differences in organismal differentials. Thus, in fishes and in urodele amphibians there is not yet any effect noticeable which could be attributed to differences in individuality differentials. How-

ever, there is even here some indication that exchange of tissues, with different race differentials, may lead to a slight and delayed lymphocytic reaction. It is only from the anuran amphibians on, that the existence of individuality differentials can be discerned. This finer reaction remains recognizable in reptiles and in warm-blooded vertebrates. We have to deal, in these cases, not only with the lymphocytic reaction, which is present also in these lower organisms, but with a desequilibrization between neighboring tissues as well, similar to that observed in the guinea pig, in consequence of which one tissue, either that of the graft or of the host, invades the neighboring tissue and replaces it; furthermore, owing to the unfavorable effect of organismal differentials, an increased keratinization may take place on the part of the transplant. Certain tissues seem to be more sensitive in this respect than others; thus, white skin in the guinea pig seems to be more sensitive than pigmented skin. In other instances, changes in pigmentation similar to those observed by Sale, may take place, as the result of differences in organismal differentials, also in lower classes of animals. Furthermore, the ingrowth of nerves from the host to the transplant may be influenced by the character of the individuality differentials of host and transplant; thus, in chameleons the nerves grow into autotransplants and make possible subsequent normal color changes, whereas they do not grow from the host tissue into homoiotransplants. In addition, if the differences between organismal differentials are more pronounced, as after heterotransplantation, there may be noticeable a direct injurious action of the host on the graft, as evidenced by primary degenerative processes in the transplanted surface epithelium and glands.

Not only the epidermis, but also the cutis, may invade the neighboring tissue; but this reaction may be caused by tissue differentials, in particular by metabolic differences which exist between pigmented and unpigmented skin. Of course, it must be conceded that, even if an invasion of pigmented skin by neighboring pigmented skin, or of white skin by neighboring white skin, should take place, it would be difficult to recognize such processes.

To summarize the various observations, we may state that in different classes of animals the mode of reaction differs. Thus, in some cases, the difference in tissue differentials is sufficient to call forth an invasion by the neighboring tissue, as we found in the guinea pig. In other kinds of animals, there must be a difference in organismal differentials and it is only on this basis that differences in tissue differentials lead to marked reactions. These latter may sometimes occur after a relatively

short period of time; in other cases, a long period of latency may intervene between the transplantation and the invasion of the neighboring skin. In the latter instance, we have evidently to deal with a cumulative effect of the strange differentials. Again there are species of animals in which, notwithstanding the differences in organismal and tissue differentials, which exist between adjoining tissues, no invasion and substitution take place. On the whole we may state that, in the struggle between host and graft, the pigmented skin dominates over the non-pigmented skin; but the reverse condition has also been observed in certain species. Furthermore, as a rule it is the host tissue which preponderates over the transplant; still, in other cases, the transplant asserts itself and becomes the dominating element. This is true, for instance, in the guinea pig, where transplanted pigmented skin invades the neighboring white host skin, as readily as pigmented host skin invades white transplanted skin. The growth energy of transplanted skin may also vary according to the growth energy inherent in the skin of the species used, and in some cases even the skin taken from different areas of the same organism may vary in growth energy. Now it seems that the epidermis, which inherently possesses a greater growth energy, tends after transplantation to invade and replace effectively the neighboring skin. In all cases the reaction which is set in motion, through incompatibility between two neighboring tissues, takes a definite course: following a period of latency the reaction appears; then, after a certain time, the activity declines and at last comes to a standstill. Thus, in the end, a new equilibrium is established, as it exists normally, for instance, between autogenous areas of pigmented and unpigmented skin adjoining each other.

In some cases, the desequilibrization, which takes place in the transplant, as a result of differences in organismal differentials, results merely in rearrangements of cells, within the transplant itself, without leading to an invasion of the neighboring tissue. Such changes were observed for instance by Collins and Adolph.

Organismal differentials and regeneration. There remains an interesting problem, which these investigations suggest, namely, that of the initial factors underlying regeneration. By regeneration we mean the reaction which sets in, in an organism, and which leads to new or increased growth processes if a defect has been made somewhere in the body, for instance, in the skin. In this sense we may consider the invasion of neighboring skin, which follows desequilibrization between transplant and host, as a regenerative process. It is generally assumed that re-

generative processes are set into motion by mechanical changes in tissue tension, which are produced through the removal of contiguous tissues. Haberlandt, however, suggested that substances are given off by necrotic material at the margin of the wound; these he designated as necrohormones, and he attributed to them the function of inducing the regenerative growth processes. Now, we have seen that epidermis can move into adjoining epidermis, which differs from it in the constitution of the organismal or tissue differential. Furthermore, we have seen that such reactions may occur after a long period of latency and may lead to the substitution or casting off of the transplant. It is very probable that, in this case, it is not the mechanical factor, which primarily elicits the response on the part of the neighboring tissue, but that incompatible substances are active and, owing to differences in differentials, they assume the function of toxins and then set into motion the reaction chain, which results in regeneration. Conversely, we may assume that, under normal conditions, there act on cells the organismal differentials of neighboring cells, which are of the same character as their own differentials; these are the normal autogenous contact substances, which are responsible for the relative quiescence of tissues, which latter thus behave in a normal manner. If these autogenous contact substances are removed, as happens when a defect in the skin is made, the same reaction must take place as after grafting of tissues possessing a different organismal differential; in both cases, either the restraining action of normal autogenous contact substances is removed, or the stimulating effect of strange differentials is substituted for the latter. Desequilibrization follows and regeneration begins to take its course. It may be mentioned here that certain experiments which have been made in invertebrates, concerning the effect of certain grafts on regenerative processes, are likewise best explained on this basis. However, we may add that acceptance of this explanation does not necessarily exclude the possibility that, under certain conditions, also purely mechanical factors may cause tissue desequilibrization, and thus initiate regenerative processes.

Organ transplantation by blood vessel anastomosis and organismal differentials If whole organs such as thyroid, kidney and ovary, or the limbs are transplanted in mammals by blood vessel anastomosis, either to another place in the same individual or to another individual of the same species, the whole transplant is perfused at once by the blood of the host and may thus remain alive, in toto, while if we apply the usual mode of transplantation, the transplant is at first nourished

merely by body fluid diffusing from the surrounding tissue towards it, and consequently the central part of the transplant, which is least nourished, becomes necrotic. Such transplantations by blood vessel anastomosis were first carried out by Höpfner (1903) and subsequently by Carrel and Guthrie, and by Carrel, who improved the method of blood vessel anastomosis used in these experiments, as well as by Lexer and others. Now it is of interest to determine, whether with this changed technique of transplantation, the organismal differentials manifest themselves and to what consequences a difference in differentials between host and transplant leads under these conditions. Although in his earlier experiments, Carrel seems to have assumed that homoiotransplantation, if this method is used, would succeed, subsequently the work of Lexer and especially that of Borst and Enderlen has shown that a marked difference exists between auto- and homoiotransplantation, even if the transplant is joined to the host by means of blood vessel anastomosis. While the former type of transplantation may succeed and the autotransplant may remain alive for a relatively long period of time,—although even in this case abnormalities in position and function of the graft may lead to secondary injuries,—the homoiotransplant usually dies within the first three weeks. Apparent exceptions to this rule,—as when it is maintained that homoiotransplanted kidney may function for several weeks,—are in all probablity due to the fact that in such cases we had to deal with syngenesiotransplantation. This is another example that demonstrates how important it is to distinguish sharply between the latter type of transplantation and the ordinary homoiotransplantation, and that the lack of this distinction makes it difficult to evaluate properly the significance of certain experiments.

The important question as to the mode in which the difference in organismal differentials influences the results in homoiotransplantation by blood vessel anastomosis, can be answered only very incompletely at the present time, owing to the difficulty of studying, in these experiments, the sequence of events following syngenesio- and homoiotransplantation. However, we know, especially through the investigations of Borst, that vessels at the site of anastomosis between host and transplant, are more often occluded by thrombi in case of homoio- or syngenesio- than in case of autotransplantation. This is presumably due to interferences with the union of the wounds in the vessel at the place of anastomosis, and to the imperfect covering of the wound by endothelium, if homoiogenous vessels adjoin each other. These imperfections in

union give rise to thrombosis. It is also possible that the surface properties of endothelial cells, or of the blood plates and leucocytes, passing such defective places with the blood, are affected in such a way that the cells become sticky under the influence of the strange individuality differentials. Probably owing to this increased occurrence of thrombosis after syngenesio- and homoiotransplantation, we may find under these conditions, more frequently, necrosis and infarcts in the graft than after autotransplantation, and these changes may precede the complete death of the transplant. As to differences in the behavior of the connective tissue and the lymphocytes at the point of junction between transplant and host, we have no definite knowledge at the present time; and we must consider, therefore, the possibility that the activity of these tissues, in case of syngenesio- and homoiotransplantation, may interfere with the circulation and the satisfactory union between host and transplant, and thus play a rôle, in addition to the other factors which we have discussed.

In this connection we may briefly refer to the transplantation of rings of blood vessels into defects in blood vessels. We find here, in principle, the same conditions as after transplantation by blood vessel anastomosis. As especially Borst and Enderlen have shown, after autotransplantation, the transplanted vessels may remain alive; veins may even be transplanted into defects in arteries and here undergo structural and functional adaptive changes. Also elastic tissue may be newly formed in the intima of vessels. But after homoiotransplantation, again thrombi are more common than after autotransplantation, and their occurrence is the rule after heterotransplantation. According to Borst, the homoiotransplanted vessels do not remain preserved but are gradually replaced by invading host tissue; the respective rôles of lymphocytes, connective tissue and capillaries do not seem to have been analyzed under these conditions. On the other hand, it has been maintained by Ingebrigtsen that, in cats, homoiotransplanted pieces of carotid arteries may remain alive as late as 3 months following operation. However that may be, the effects of organismal differentials manifest themselves in blood vessel transplantation in a new way, which seems to be characteristic of this type of transplantation.

Parabiosis and organismal differentials. In transplantation by blood vessel anastomosis, the body fluid of the host perfuses the vessels immediately after the operative procedures have been completed. Under these conditions, the strange body fluids of the host act therefore almost immediately and with great intensity on the transplant. The tissue

reactions, on the other hand are, as far as the transplant as a whole is concerned, much diminished, although they may make themselves felt at the point of union between transplant and host.

In certain respects, parabiosis, a method of transplantation which in principle was used already by P. Bert, but was developed in its present form by Sauerbruch and Heyde, represents a type of transplantation, in which we find the reverse condition from that obtaining in transplantation by blood vessel anastomosis. In parabiosis the union between two organisms is less complete than in the case of ordinary transplantation, where relatively small pieces of tissue are completely severed from the original bearer and transplanted, either into a pocket, or on the surface of the new, and more or less strange, host. The ordinary transplant is thus exposed to the body fluids of the host, acting by diffusion, as well as to the direct action of the cells of the host. The transplant is more or less at the mercy of the host. In parabiosis, on the other hand, two organisms are usually united to each other by means of skin and peritoneum. Each organism continues to take its own food, to maintain its own metabolism; each is united with its partner, mainly by means of capillary anastomoses, which gradually develop; occasionally, though, there may be an additional connection through large vessels in the omentum. At the point of union, there may also take place an interaction of the tissues of both partners, which is, however, restricted to a relatively limited area in each organism. The partners, corresponding to host and transplant, are therefore largely, although not entirely, independent of each other; yet, a not very intense, but continuous exchange of strange body fluids occurs. It is of great interest to determine whether, under these conditions, the strange organismal differentials can make themselves felt.

Similar to parabiosis, as far as the relative independence of transplant and host is concerned, is transplantation by the flap method, in which an organ or piece of tissue is partly joined to another point of the same, or of another, organism, at the same time still maintaining its old connections. While the transplanted skin flap is thus exposed to the influence of the host, it is essentially nourished by the blood of the organism in which it originated and with which it remains connected by a wide bridge of tissue, thus having with it a common individuality differential. Parabiosis is a skin flap union, (to which is usually added peritoneal union), in which two whole organisms, instead of parts of organisms, are joined to each other. If autotransplantation is carried out by the flap method, the transplant heals in, usually, in its new place,

and in general remains united with the new host, even after the connection with its own organism has been severed by cutting the pedicle. However, if the flap was homoiotransplanted, the graft may remain in good condition, as long as it is still connected with its own organism; during that period it is sufficiently under the influence of autogenous substances to be able to resist the action of homoiotoxins, which develop at the point of union. But as soon as the pedicle connecting the flap with its own organism has been cut, and the transplant is exposed to the full influence of the new host, the effect of the homoiotoxins becomes potent, and the results are ultimately the same as though an ordinary homoiotransplantation had been carried out from the beginning. The advantage gained by the flap method was merely temporary. These facts apply to skin, as well as to other organs, if transplanted by means of a pedicle.

In parabiosis the result is, in principle, the same as in flap transplantation; a certain protection is furnished the partners, but ultimately the differences in individuality differentials which exist between them lead to incompatibilities, which become more and more accentuated, until in the end one of the partners succumbs. The incompatibility may result in the termination of the parabiosis as early as 9–14 days after the connection has been made, or, in very favorable cases, the union may last as long as 9–12 months (Morpurgo). It is important to realize, in cases of parabiosis, that, though there is established an anastomosis of blood capillaries between the two partners, this does not imply that the latter have become one and the same organism, as far as their body fluids are concerned. There is reason for assuming that constantly a small amount of blood and of peritoneal and interstitial fluid passes from one partner into the other, and that here it is mixed with a much larger quantity of the animal's own fluid. It reaches, therefore, the cells of the strange organism, at best, only in very great dilution and, before it comes into actual contact with the cells of the partner, it meets a current of fluid from the latter, passing in the opposite direction, namely, from the cells towards the capillaries. The tissues thus continuously create anew their own differentials, which meet the very diluted strange differentials, in such a way that a gradient of these differentials develops. Hence the action of the body fluids of one partner on the other is very imperfect. Accordingly, we notice that specific substances, produced in the one partner, affect this individual usually stronger and earlier than they do the other partner. This is true, for instance, of the conditions following extirpation of the kidney of one

partner, or of experimentally produced ileus. After the former procedure, edema and cardiac hypertrophy seem to develop in this individual only. Likewise the effects of interference with the sex organs, as far as they are regulated by hormones, are only incompletely transferred from one partner to the other. Correspondingly, if two animals, one susceptible to a certain homoiogenous tumor, the other one non-susceptible, are joined together by parabiosis, each organism preserves its own characteristic susceptibility. Each of the parabiotic individuals continues, therefore, to a certain extent, to live its own life. In some respects, parabiosis represents, thus, an intermediate condition between auto- and homoio- or syngenesiotransplantation, each organ and tissue receiving the autogenous substance produced in its own body, as well as homoiogenous or syngenesio-substances from the partner.

In typical cases of parabiosis, there is at first a so-called harmonious period, in which both partners do relatively well; this is followed sooner or later by a disharmonious period, in which one of the partners becomes weak, atrophic and eventually dies. However, also the surviving, dominating partner is usually not quite so strong, as it would have been if it were independent. In this disharmonious state, the tone of the blood vessels is lowered in the weaker partner and the stronger partner therefore pumps a considerable part of its blood into the weaker one, which thus becomes hyperemic and shows polycythemia, while the dominating partner, on the contrary, becomes anemic. It is of interest that there may occur, in the stronger partner, a hyperplasia of the lymphatic tissue and a stimulation of the mesenchymatous tissue in general, and that also its bone marrow may show the effects of stimulation, while in the weaker partner, after a transitory period of stimulation, an atrophic condition of the bone marrow usually occurs, which may end in a state of fibrosis.

What is the cause of the disharmony which develops often in the second or third week after the union has been established, but which in other cases may develop much later? It seems that accidental factors determine which of the two partners will ultimately be suppressed, and apparently it is usually the one which in some way was the weaker at the time when the union was established. Various causes have been suggested for the disharmony which in the end always develops. Thus athrepsia has been considered, the assumption being that the stronger partner deprives the weaker one of foodstuffs. This interpretation is probably not correct, because the weaker partner often consumes an abundant amount of food and the stronger partner also loses somewhat

in weight. Many authors assume that a state of chronic anaphylaxis develops from the consequences of which the weaker partner suffers. The dilatation of the vessels, which is observed in the latter, is usually cited as the main argument in favor of this view; however, this condition of the vascular system may be due to general weakness rather than to specific anaphylaxis. Besides, there are several facts which speak directly against the idea that a state of anaphylaxis is the cause of disharmony; thus it has not been possible to demonstrate the production of antibodies, like hemolysins, agglutinins or precipitins in parabiosis. It is therefore not probable that sensitizing antibodies develop, under these conditions, in such a quantity that they can be of great significance. Furthermore, if the two partners, during the stage of disharmony, are separated, a recovery of both may take place. If subsequently one of the partners is again united with a strange individual, no sign of hypersensitiveness becomes noticeable. A still better demonstration would be, to unite the same individuals with each other a second time; however, this experiment does not seem to have been made.

The disharmonious condition has also been attributed to the passing of ordinary metabolic products from one individual to the other. The increased toxicity of the urine in the parabiotic animals has been attributed to this factor. However, such metabolic products develop normally and, as far as we know, they are approximately the same in all normal individuals of the same species. It is therefore not probable that they are the principal cause of disharmony.

There remains still one factor which has to be considered, namely, the possibility that substances, which carry the individuality differentials and which therefore distinguish different individuals of the same species, are given off in small quantities, by the metabolizing tissues of one organism, and enter the circulation of the other, although it is not possible to demonstrate such an occurrence by the methods which can be used in the case of hetero-differentials. Such substances might be responsible for the gradually developing disharmony, and they might also stimulate the lymphocytic and reticulo-endothelial system of the partner, in correspondence with the stimulation of lymphocytes which is found in ordinary homoiotransplantation. Thus these homoiotoxins may function as very slowly acting toxins. In favor of this view, we may mention also the fact that the stage of disharmony develops generally the earlier and is the more intense, the less nearly related the partners are. This is quite evident, if rabbits are used for parabiosis; but it seems also to be the case if white rats are used, which are the animals

peculiarly suitable for parabiosis. However, secondary factors play a rôle also. Thus it has been found that it is not sufficient to unite individuals belonging to the same litter, but that it is preferable to use young animals and those having the same sex. In general, parabiosis between different species does not succeed, although Lambert succeeded in joining young rats and mice together, however only for a very short time. At most, they remained united for eight days. Even a guinea pig and rat could in one case be joined together for eight days; however, under these conditions, no real wound healing occurred at the point of union.

Of special interest from our point of view are the experiments of Majeda; he transplanted skin from one rat to another, preceding and following parabiosis. He found that those animals, between which skin could be readily exchanged and healed on, at least temporarily, were more suitable for parabiosis than other animals, in which skin transplants did not grow on, in a satisfactory manner; in the former, the disharmony appeared later than in the latter. This is further proof of the conclusion that the character of the individuality differentials determines the outcome of parabiosis, and that differences in individuality differentials in partners are the cause of the disharmonies which develop sooner or later. Majeda found in addition, the interesting fact that parabiosis does not improve the chances of homoiotransplantation of skin; on the contrary, skin transplanted from one partner into the other partner seems not to grow as well as when the two animals are unattached. Even autotransplants do not grow as well in parabiosis. It is possible that circulating homoiotoxins may injure even autotransplants under these conditions; but it is also possible that other abnormalities of a non-specific character, developing in parabiosis, may be responsible for this result. As may be expected, direct blood vessel anastomosis, which has been attempted in a few cases in parabiosis and which may succeed for a short time, does not improve the fate of the partners or of skin transplants to any marked degree.

We may then conclude that, in all probability, individuality differentials are primarily responsible for disharmonies developing in parabiosis. It is however possible that, secondarily, incompatible differentials may lead to further metabolic abnormalities, and among them anaphylactic conditions, although the latter have not so far been demonstrated. There are some indications that also, locally, at the point, where the tissues of the partners are joined together, organismal differentials influence the interaction of tissues.

Within the first week, the tissues of the parabiotically united animals grow towards each other; these tissues consist mainly of fibroblasts—including perhaps other types of mononuclear cells—endothelia of blood and lymph vessels and polymorphonuclear leucocytes. Where they meet, they form one homogeneous granulation tissue, in which it is impossible to separate from each other the cells coming from the two partners. Also the capillaries meet and make connections. Subsequently, after the completion of the first week, the granulation tissue gradually becomes transformed into scar tissue, which contracts, exerts pressure on the capillary vessels and thus interferes with the exchange of blood, lymph and interstitial fluid at the point of junction; from now on the two partners are usually joined together by granulation tissue, but the epidermis seems only rarely to heal completely over the wound. This may however perhaps take place, if the individuality differentials of both partners are more nearly related. In case of disharmonious parabiosis, the union of the skin flaps may be only temporary. The occurrence of ulceration and infection seems to be especially common under this condition. Also the union of blood vessels of the two partners seems to take place in a more satisfactory manner when the parabiosis is harmonious.

Thus, we have definite indications that also as far as the local reaction is concerned, the character of the organismal differentials enters as a factor into the interaction of the two partners. It is probably owing to the strangeness of individuality differentials, at the point of union, that the connective tissue formation here is more abundant than it is in the case of ordinary wound healing. Presumably we have to deal with a stimulation of fibroblast activity and subsequent formation of much fibrous tissue, under the influence of homoiotoxins. We would then find here, the same effect of homoiotoxins on connective tissue, which we noted in ordinary homoiotransplantation. On the other hand, we found no indication from the literature that there is a local increase in the activity of lymphocytes under these conditions. However, a thorough study of the successive stages in wound healing, at the point of junction of the two partners, has apparently not yet been made.

Of interest in this connection is an experiment of Morpurgo, in which this investigator showed that it is possible for a peripheral nerve to grow from one into the other partner and here innervate the muscle tissue and connect with the skin of the strange animal. Homoiotoxin action evidently does not prevent this process from taking place, provided the scar tissue, which otherwise might oppose it, has been excised.

Organismal differentials and tissue culture. We have seen that differences in individuality differentials, after transplantation, manifest themselves in reactions of cells and tissues of the host against the transplant, and that direct effects of homoiotoxins, circulating in body fluids, are indicated only in the case of certain sensitive tissues. In accordance with these facts we find that if we cultivate mammalian tissues in serum or blood plasma, in vitro, no special difference in the effect of homoiogenous serum or plasma, as compared with an autogenous medium, is noticeable. Thus Miss I. T. Genther and the writer compared quantitatively the mitotic activity of guinea pig thyroid—counting for this purpose the number of mitoses—in autogenous and homoiogenous serum of the same species. No marked difference in the mitotic proliferation of acinus cells was noticeable in these two media, although we should expect that quantitative differences in mitotic activity would provide a delicate indicator of the influence of homoiotoxins. However, a certain reservation is necessary here inasmuch as we must consider the fact that conditions in vitro and in the body are different, not only as far as the absence of host tissues is concerned, but also in regard to the quantity of blood plasma or serum present in the medium which is able to act on the transplant. In the body, a continuous current of fluid is carried to the strange tissues and the homoiotoxins, as far as they circulate in the blood, are constantly being renewed, so that a fresh supply is alway acting upon the transplant. In vitro, on the contrary, a relatively small amount of the fluid constituents of the blood surrounds the piece of tissue for several days, and the amount of homoiotoxins thus available is soon exhausted. Similarly, we find the difference between the effects of homoiogenous and heterogenous plasma on tissue growing, in vitro, much smaller than the differences between the changes in the graft following homoio- and heterotransplantation. Thus Lambert and Hanes found that tumor cells, as well as normal spleen tissue, show a relatively slight sensitiveness to the toxic action of heterogenous serum, although some variations exist in the action of different sera. And even a culture of fibroblasts can, for a certain time at least, remain active in a heterogenous medium, although the injurious action of the latter becomes manifest more readily in the case of fibroblasts, than in the case of tumor tissue (A. Fischer). The same reservations, of course, hold good here, as in the case of homoiogenous plasma or serum, concerning the small amount of serum or plasma, which is active under these conditions. In accordance with these observations, it has been found, furthermore, that even the homoiogenous plasma of an animal,

which has shown itself to be immune to the growth of a certain kind of a tumor, may still serve as a culture medium for such tumor cells growing in vitro. We see then that the tissue culture method is, on the whole, not a sensitive method for the detection of differences in organismal differentials.

Organismal differentials as normal constituents of the body and their significance in specific adaptation. Transplantation as a method of investigation made possible the analyis of the organismal differentials. We have so far studied them and observed their effects by subjecting pieces of tissues to the action of the strange differentials of the host. We shall now show that organismal differentials play also a rôle in the interaction of substances and, therefore, in certain biochemical processes, within the normal organism, as well as under experimentally produced abnormal conditions, and, in particular, that it is due to their presence that we apply the attribute "specific" to certain substances and processes in the living organism. For this purpose it will first be necessary to analyze the term specific as it is used in biological processes. In general, we may distinguish three different meanings of this term. 1. It may mean that a certain process, or a certain structural element, in a living organism, is connected with, or is dependent upon, a characteristic substance, without reference to any relation of the latter to organismal differentials. 2. It may mean that a certain constituent or process in an organism is characterized by a substance possessing an organismal differential. 3. It may mean that a substance in an animal carries an organismal differential and, by means of the latter, enters into relations with another substance in the same or in another animal, nearly or distantly related, which carries the corresponding organismal differential, and on account of the similarity or identity of the differentials, these two substances interact with each other more readily than they would with other substances, which are the bearers of dissimilar organismal differentials. In the latter kind of reaction, two substances are more or less specifically adapted to each other, on account of a correspondence of the organismal differential entering into the constitution of these substances.

Organismal differentials and the structure of organisms. Specific adaptation can most readily be demonstrated, in case two substances carry the same class or generic differential. The finer the differentials are, which may come into play, the greater becomes the difficulty in demonstrating a specific adaptation. Thus, a specific adaptation between substances carrying species differentials can be demonstrated

with greater difficulty, than an adaptation between substances carrying class or generic differentials; and still greater is the difficulty in demonstrating a specific adaptation, depending on an interaction between individuality differentials. This graded difficulty, in demonstrating the action of organismal differentials, depends upon gradations in the fineness of the reactions which they cause. We need very finely graded sensitive processes, in order to demonstrate individuality differentials. The cellular reactions, which we have studied in transplantation, represent the finest reaction which has so far been discovered, for the analysis and differentiation of organismal differentials. That which we have just stated, concerning the rôle organismal differentials play in primary processes, in which we have to deal with preformed specific substances, is paralleled by the part these substances play in immune processes. Immune reactions likewise can be demonstrated the more readily the coarser are the differentials which serve as antigens. Differences in the finer differentials, in particular, the individuality differentials, either cause insufficient disturbances, after their introduction into a strange individual, or they are entering into relationship with so great a number of other substances, that the specific effects which they may cause, are somehow covered up.

We may mention a few examples of specific adaptation due to the interaction of organismal differentials. It can be shown that there exist, in blood sera, substances which, when combining with substances in tissue extracts, cause either an acceleration or an inhibition of blood coagulation. Both of these substances, the accelerators as well as the inhibitors, carry class or species differentials, and when substances carrying the same differential interact, the effect is greater than when substances carrying disharmonious differentials interact. It can furthermore be shown that, in the various organs of a certain class or species of animals, substances, which can be extracted from the tissues, carry the same differential. This is true of the tissue coagulins, as well as of the inhibiting substances or their precursors.

In a similar manner, leucocytes are specifically adapted to blood serum of their own kind, as evidenced by the readiness with which various sera facilitate phagocytosis on the part of the leucocytes. The bacteriotropin of the serum of an animal species is specifically adapted to the leucocytes of this species. Evidently substances, which participate in in this function, bear the species differential and such substances are present in the serum as well as in the leucocytes.

In invertebrates also, species or class differentials may take part in

certain processes. Thus, the egg secretions act in a specifically adapted manner on spermatozoa of the same species; the agglutinating substance, in the egg secretions, carries the species differential and acts on a corresponding differential substance in the sperm.

Groups carrying the organismal differential may also be concerned in enzyme action. Thus, according to Hedin, in infusions of gastric mucosa, a substance inhibiting the action of rennet can be obtained, which carries the species or class differential and which must correspond to the differential substance which is attached to rennet itself. Similarly, according to Harvey, luciferase, the enzyme which, in interacting with luciferin, causes luminescence, differs in different classes of animals, and luciferin and luciferase when derived from the same type of animals, produce the greatest effect; we may therefore, conclude that both of these substances carry the species differentials.

If instead of considering class and species differentials, we turn to individuality differentials, we have greater difficulty in demonstrating their presence and their activity. But there can be no doubt that they are present in all organisms, at least in all the higher organisms. As we have tried to show in this paper, they can be readily demonstrated through transplantation and they must play a very important rôle as autogenous tissue regulators,—contact substances,—active in every higher organism; as stated, they can be demonstrated even in certain protozoa. In some cases their presence can be detected also by means of serum reactions, as in experiments of Todd with the production of immune isohemolysins, to which we referred above. His observations permit the conclusion that, even in mammalian erythrocytes, substances carrying the individuality differential must be present and may call forth the production of antibodies, which are similarly carriers of the individuality differential. In this connection, it may be well to suggest that the same terms be used in all cases, in order to express the fact that individuality differentials enter into certain reactions; they do so in homoiotransplantation and they likewise play a rôle in case we have to deal with isohemolysins, isoagglutinins, whether preformed or produced through immunization. It might be well to adopt the prefix "homoio" in all instances in which individuality differentials enter into a reaction.

At this point we may also refer to the recent investigations of Zangemeister, who maintains that, by means of a delicate technique, one is able to demonstrate a specific change in the colloidal state of protein micellae, if the serum of a newborn child is mixed with the serum of either father or mother, whereas, with the serum of a strange individual,

the reaction is said to be lacking. If in the future, these findings should be confirmed, then we should have to deal with a specific interaction of substances carrying individuality differentials, but with a syngenesio— rather than with a homoiogenous character.

Each organism thus contains material which possesses these organismal differentials. The latter play a part in various functions, but their rôle so far has been analysed only very incompletely. We have seen that the method of transplantation can be very useful in the analysis of these relationships. But at the same time we wish to point out that, in the usefulness of this method, certain limitations exist which have to be considered in determining whether a certain substance does or does not carry an organismal differential. Thus, for instance, if it is possible to transplant successfully a certain part of an organism into an organism belonging to a different class, genus or species, it is evident that in this case the respective differentials either are not developed, or that they do not call forth antagonistic reactions on the part of the host, or that the transplant is very resistant to such injurious reactions. If, then, under these conditions, the transplant interacts with the host in a definite way by means of certain substances, we are not justified in drawing the conclusion, as has generally been done in the past, that these substances are not "specific" by which was meant that they do not possess organismal differentials. Tissues as well as the substances still may carry the differentials, but even strange differentials may be effective or the differentials may be less individualized. Only if such substances can be separated from the tissues and show undiminished activity in cases in which the incompatibility of organismal differentials in host and graft prevents successful transplantation, may we conclude that the substances do not possess organismal differentials. We may cite certain hormones like thyroxin or adrenalin as devoid of organismal differentials. On the other hand, if a tissue can still be transplanted into a different genus, but after such a transplantation does not exert a certain function, whereas it exerts this function after transplantation into a different species, we may conclude that such a substance carries a generic differential.

To cite some examples, if, after transplantation of a piece of embryonic material into an embryo of a different species, genus or class, the transplant lives, exerts its function as an organisator—contact substance, in the manner that has been established by Spemann and his associates, then we cannot exclude the possibility that these organisators may possess the same organismal differential as the embryonic tissue which

was used for transplantation. The same consideration applies to the substances which induce metamorphosis in amphibia. By means of transplantation, Weigl, Uhlenhuth, Kornfeld and Lindeman have proven the existence of such substances. These substances likewise may or may not carry the same organismal differentials as the transplanted tissue.

Organismal differentials in their relation to other specific constituents or reactions of organisms. There are certain other complications in these problems which we have to consider. As we have seen, there are strong reasons for assuming that organismal differentials and, in particular, individuality differentials are combinations of many substances. They are either independent of each other, or are at least distinct chemical groups, which may be combined with other substances (carriers). Now, there are, in addition, groups of individuals, which have certain other characteristic inheritable substances in common, as, for instance, those substances which cause the iso-, or better designated homoio-agglutination of erythrocytes. These substances are much simpler in their constitution than the individuality differentials. By means of these, individuals as such are not differentiated, but only four groups of human beings; and somewhat similar groups may be distinguished among certain anthropoid apes. In this respect, these substances differ then from the real organismal differentials, but they resemble the latter in distribution, in that these same characteristic substances, which are found in the erythrocytes, are present in almost all the tissues of the individual. The blood group agglutinable substance is therefore a characteristic common to all the cells of the body. Nevertheless it is not identical with the individuality differential, but it may be that the blood group agglutinable substances are constituent parts of the individuality differentials. In analyzing specific adaptations we must consider the possibility that in certain cases they may not depend upon the interaction of the complete organismal differentials, but rather on the presence of partial differentials, comparable to those determining the blood groups or even more simple in constitution than the latter.

For the reasons stated, it is therefore inadvisable to identify blood-groups with the constitution of an individual. The inheritable constitution of an individual is a much more complex condition; it is largely determined by the individuality differential, but in addition by characteristics which are apparently dependent upon the interaction between individuality or other organismal differentials and tissue (organ) differentials. As to the other inheritable characteristics, which have

been used to differentiate individuals, as for instance, the skin patterns, (finger prints), they depend apparently upon the interaction of a number of diverse factors; they are strictly localized characteristics, quite distinct from individuality differentials. The same observation holds good, presumably, as far as the individual or species smells are concerned. In addition, there enter into the constitution of organisms, factors which do not tend to distinguish animal species from each other, but which are common to the most heterogeneous groups of animals, namely, the heterogenetic or heterophilic (Forssman) antigens. They are, of course, entirely distinct from the heterodifferentials, which characterize different species of animals. In a certain sense, the heterogenetic, Forssman antigens are the opposite of the heterodifferentials; the latter characterize, in a graded manner, according to their relationships, different species and separate them from one another, whereas the Forssman antigens tend to bring together quite unrelated species.

We have already referred to the differences existing between organismal and tissue differentials, and we have mentioned that there are indications that these two sets of differentials or rather their precursors may, under certain conditions, interact and coöperate in building up the organisms. However, the tissue differentials also need a sharper definition and must be separated from related conditions. Thus in our discussion of the transplantation of pigmented and unpigmented skin, we had to distinguish between the effects of organismal differentials and what we then designated as tissue differentials. By the latter term, we understood in this case the difference in constitution between pigmented and unpigmented skin. However, in a strict sense, there is no tissue differential of skin, but there are tissue differentials of epidermis and cutis. By the tissue differential of the epidermis, we should understand the substance or the substances which are common to the epidermis of different species of animals, and which differentiate the epidermis, for instance, from the underlying cutis, which latter also has factors, namely, tissue differentials, in common in various species of animals. If we further distinguish between the tissue differentials of pigmented and unpigmented epidermis, we are extending this term and we must realize that we no longer apply it in the strict sense. However, there are apparently associated, with the presence or absence of pigment in the epidermis and also in the cutis, certain other differences in the reactions of these respective tissues, which indicate that we may have to deal not merely with the addition of melanin pigment to the skin epidermis or cutis, but with further-going characteristic differences, which

may possibly be held in common by the pigmented epidermis of different related species, and which differ from the characteristics of unpigmented epidermis.

In conclusion, we may point out that the term "individuality" as it is commonly used, signifies primarily a psychical-social unit. It is the psychical characteristic of a higher organism which distinguishes it from other organisms within the same social group. There is reason for assuming that the psychical characteristics of individuals, strains and species, as far as they are inherited, be they reflexes, instincts or modes of thinking, may somehow be dependent upon the real organismal differentials. If, for instance, animals belonging to the same species associate together, while those belonging to other species do not do so, there are at work complex systems of reflexes, into the shaping of which ultimately organismal differentials have entered, at least as one of the determining conditions. In this sense, we have in the case of these phenomena to deal with derivatives of the organismal differentials. It is quite natural that primarily our concept of individuality is based on these psychical characteristics, which are derivatives of the underlying organismal differentials, because, in the case of psychical reactions, we have to deal most directly with our own experiences, as distinct from those of surrounding, otherwise related organisms. In our original concept of individuality, we started, therefore, with the derivative condition and gradually progressed to the analysis of the underlying condition, namely, the organismal differentials.

BIBLIOGRAPHY

ABDERHALDEN, E. 1914. Lehrbuch d. physiol. Chemie, II. Aufl. Wien, Urban und Schwarzenberg.

ADDISON, W. H. F. AND L. LOEB. 1913. Beiträge z. Analyse d. Gewebewachstums. X. Über d. Beziehungen zwischen Struktur d. Epidermis d. Taube u. d. Meerschweinchens u. d. Proliferation d. normalen u. regen. Epithelzellen. Arch. f. Entwicklgsmech., xxxvii, 635.

APPEL, F. W. 1929. Testis grafts in ovariotomized fowls. Journ. Exper. Zoöl., liii, 77.

AXHAUSEN, G. 1909. D. histol. u. klin. Gesetze d. freien Osteoplastik auf Grund v. Tierversuchen. Arch. f. klin. Chirurgie, lxxxviii, 23.

BALDWIN, H. A. 1920. Skin grafting. Med. Record, xcviii, 686.

BAUER, K. H. 1927. Homoiotransplantation v. Epidermis bei eineiigen Zwillingen. Beiträge z. klin. Chirurgie, cxli, 442.

BAUER, K. 1929. Beitr. z. Frage d. Makrophagengenese im entzündeten Gewebe bei vitalgespeicherten Tieren. Zeitschr. f. Zellforschung u. Mikrosk. Anatomie, ix, 155.

BECHER, H. 1928. Blutuntersuchungen an Parabioseratten. Verh. d. anat. Gesellsch., xxxvii, 227.

BIRKELBACH, W. 1911. D. Wirkung doppelseitiger Nierenextirpation b. Parabiose Ratten. Zeitschr. f. experim. Pathol. u. Therapie, viii, 465.

BORN, G. 1896–1897. Über Verwachsungsversuche mit Amphibienlarven. Arch. f. Entwicklgsmech., iv, 350.

BORST, M. 1913. D. Verpflanzung normaler Gewebe. XVII. Internat. Congress of Medicine, London, Oxford Univ. Press.

BORST, M. 1913. Grafting of normal tissues. Brit. Med. Journ., ii, 1383.

BRAUS, H. 1906. Über d. biochem. Verhalten d. Amphibienlarven. Arch. f. Entwicklgsmech., xxii, 564.

BRÜDA, B. E. 1929. Über Beziehungen d. Milz z. Tumorwachstum. Münch. Med. Woch., No. 40, 1671.

BRÜDA, B. E. AND H. PFEIFFER. 1929. Über d. Bedeutung d. Milz z. d. Speichezellensystems (Reticulo-endothelo) für d. Abwehr in bösartigen Impfgeschülsten d. Ratte. Zeitschr. f. exper. Medizin, lxviii, 116.

BÜNGELER, W. 1927. Geschwulsttranplantation am gespeicherten Tier. Frankf. Zeitschr. f. Pathologie, xxxv, 67.

BURNS, R. K. 1923. Further observations on parabiotic amphibian larvae. Anat. Record, xxxi, 30.

BURNS, E. L., F. H. SCHARLES AND L. F. AITKEN. 1930. Interaction between substances in tissue extracts and blood sera. Effect of mixtures of these substances on coagulation of blood. Proc. Soc. Exp. Biol. and Med., xxvii, 492.

CARNOT, P. ET C. DEFLANDRE. 1896. Persistance de la pigmentation dans les Greffes epidermiques. C. R. Soc. Biol., xlviii, 178.

1896. Greffe et pigmentation. C. R. Soc. Biol., May 1, No. 14, xlviii, 430.

1896. Persistance de la pigmentation dans les Greffes epidermiques. C. R. Soc. Biol., xlviii, 178.

CARREL, A. AND C. C. GUTHRIE. 1906. Complete amputation of thigh with replantation. Amer. Journ. Med. Sciences, lxxxi, 297.

1906. Anastomosis of blood vessels by the patching method and transplantation of the kidney. Journ. Amer. Med. Assoc., xlvii, 16, 48.

CARREL, A. 1908. Results of transplantation of blood vessels, organs and limbs. Journ. Amer. Med. Assoc., li, 1662.

1910. Remote results of the replantation of the kidney and the spleen. Journ. Exper. Med., xii, 146.

CELLER, H. L. UND F. HAMBURGER. 1905. Ueber spezifische Antikörperbildung nach Eiweissfütterung. Wien klin. Wochenschr., xviii, 271.

COLE, W. H. 1922. The transplantation of skin in frog tadpoles with special reference to the adjustment of grafts over eyes to the local specificity of integument. Journ. Exper. Zoöl., xxxv, 353.

COLLINS, H. H. AND E. F. ADOLPH. 1926. The regulation of skin pattern in an amphibian dienyctulus. Journ. Morphol., xlii, 473.

CORRENS, C. 1910. Individuen u. Individualstoffe. Naturwissenschaften, iv, 193, 210.

1913. Selbststerilität u. Individualstoffe. Biol. Centralblatt., xxxiii, 389.

Corson-White, E. P. and L. Loeb. 1910. Über d. Einfluss physikalisch schädigender Agentier (Wärme) auf d. Wachstum d. Tumorzellen. Centralbl. f. Bakt. I Abt., lvi, 325.

1910. Über transplantation v. stationären u. sich rückbildenden Tumoren. Centralbl. f. Bakt., lvi, 488.

Cristiani, H. 1904. De la Greffe hétérothyroidienne. Journ. Physiol. et Pathol. gén., vi, 476.

1905. Evolution des Greffes thyroidiennes superflues. C. R. Soc. Biol., lviii, 361.

Cristiani et A. Cristiani. 1905. Evolution comparées des Greffes de jeune tissue thyroidien transplantées sur des animaux d'age different. C. R. Soc. Biol., lviii, 531.

Cristiani, H. 1904. De la Greffe thyroidienne chez les oiseaux. C. R. Soc. Biol., lvi, 192.

1903. Vitalité des tissus séparés de l'organisme. C. R. Soc. Biol., lv, 828.

Crossen, R. J. 1928. The attraction of lymphocytes by homoiotoxins. Arch. Pathol., vi, 396.

Danchakoff, V. 1919. Mesenchymal activity as a factor in resistance against mouse sarcoma in chick. Proc. Soc. Exp. Biol. and Med., xvi, 67.

1918. Equivalence of different hematopoietic anlagen. II. Grafts of adult spleen on the allantois and response of the allantois tissue. Amer. Journ. Anat., xxiv, 127.

Danforth, C. H. and F. Foster. 1929. Skin transplantation as a means of studying genetic and endocrine factors in the fowl. Journ. Exper. Zoöl., lii, 443.

Davis, J. S. 1917. Some problems of plastic surgery. Ann. Surg., lxvi, 89.

Dawson, A. B. 1920. The integument of Necturus macul. Journ. Morphol., xxxiv, 487.

Dobrzaniecki, W. 1929. Homoiotransplantation and several bloodgroups. Ann. Surg., xc, 926.

Dürken, B. 1926. D. Verhalten embryon. Zellen im Interplantat. Arch. f. Entwicklgsmech., cvii, 727.

Duschl, L. und B. Niekau. 1924. Untersuch. über d. Gefässkommunikation zwischen parabios. Ratten. D. Zeitschr. f. Chirurgie, clxxxvi, 76.

Dyke, S. C. 1922. On bloodgrouping and its clinical application. The Lancet, 579.

Eden, R. 1922. D. Bedeutung d. Gruppenweisen Haemagglutination für d. freie Transplantation u. über d. Veränderung d. Agglutinationsgruppen durch Medikamente, Narkose, Roentgenstrahlung. Deutsch. Med. Wochenschr., no. 3, 85.

Elson, J. 1929. Auto- and homoiotransplantation of cross striated muscle tissue in the rat. Amer. Journ. Pathol., v, 425.

Enderlen und M. Borst. 1910. Beiträge z. Gefässchirurgie u. z. Organtransplantation. Münch. Med. Wochenschr., no. 36, 1865.

1909. Über Transplantation v. Gefässen u. ganzen Organen. Verhandl. d. deutch. Path., Zesellschaft. xiii Tagung.

ERDMANN, R. 1923. Explantation u. Verwandtschaft. Zeitschr. f. induktive Abstammungs u. Vererbungslehre, xxx, 301.
1922. Explantation u. Verwandtschaft. Verh. d. deutschen Zoöl. Zesellsch, xxiv–xxvii, 102.
1927. Verwandtschaftsbeziehungen d. Anurenfamilien, geprüft durch Implantationsversuche gezüchteter Haut. Arch. f. Entwicklgsmech., cxii, 739.

ERNST, M. 1927. Untersuch. über hormon. Wachstumsantriebe d. Brustdrüse unter Einbeziehung d. Parabioseverfahrens. D. Zeitschr. f. Chir., ccvii, 231.

FAMULENER, L. W. 1912. On the transmission of immunity from mother to offspring. Journ. Infect. Dis., x, 332.

FELS, E. 1929. D. Einfluss d. Parabiose auf d. innere Sekretion. Med. Klinik., xxv, 557.

FICK, R. 1907. Über d. Vererbungssubstanz. Arch. f. Anat. u. Physiol. Anat., Abt., 101.

FICHERA, G. 1909. Developpement des Greffes embryonnaires et foetales. Arch. Méd. exper. et d'anat. pathol., xxi, 617.

FLEISHER, M. S. 1918. Immunity and transplantation. I. The reaction occurring about tissue transplanted into heterogenous animals. Journ. Med. Res., xxxvii, 483.
1918. Immunity and tissue transplantation. IV. The influence of immune serum upon the reaction about transplanted tissues. Journ. Med. Res., xxxix, 1.
1921. Leucocytic and fibroblastic reactions about transplanted tissues. Journ. Med. Res., xcii, 163.
1921. Heterotransplantation of lens and cornea. Journ. Med. Res., xlii, 491.
1920–1921. Autotransplantation and homoiotransplantation of cornea, iris and lens. Journ. Med. Res., xlii, 173.
1922. Immunity in relation to transplanted tissue. Journ. Med. Res., xliii, 145.

FLEISHER, M. S. AND L. LOEB. 1913. Transplantation of tumors in animals with spontaneously developed tumor. Surg., Gynec. and Obst., xvii, 203.
1916. Immune-reactions against tumor growth in animals with spontaneous tumors. Journ. Med. Res., xxxiv, 1.
1916. Further investigations on the hereditary transmission of the difference in susceptibility to the growth of transplanted tumors in various strains of mice. Journ. Cancer Res., i, 331.

FLEISHER, M. S., E. P. CORSON-WHITE AND L. LOEB. 1912. Quantitative Untersuchungen über Immunität gegen Tumoren b. Mäusen. Centralbl. f. Bakt., lxiii, 450.

FORSSMAN, J. 1929. Einige Immunitätsfragen im Lichte. d. heterogenet. Forschung. Wien. Klin. Wochenschr., xlii, no. 20, 669.

FRANGENHEIM, P. 1910. Dauererfolge d. Osteoplastik im Tierversuch. Arch. f. Klin. Chir., xciii, 190.

GASSUL, R. 1922. Homopl. Transplantation v. Explantaten aus erwachsener Froschhaut. Deutsch. med. Wochenschr., xxxv, 1163.

1923. Experimentalle Studien über Auspflanzung Überpflanzung und Regeneration von Explantaten aus erwachsener Froschhaut. Arch. f. Entwicklgsmech., lii, 400.

GIARD, A. 1896. Y-a-t-il antagonisme entre la Greffe et la regéneration. C. R. Soc. Biol., iii, 180.

GODLEWSKI, E. 1922. L'hérédité dans lés cellules végétatives au cours de la regéneration chez l'axolotl. Note prelim. bullet. de l'acad. pol. de Cracovie (Cit. from KOLODZIEJSKI).

1928. Untersuchungen über d. Auslösung u. Hemmung d. Regeneration beim Axolotl. Arch. f. Entwicklgsmech., lxiv, 108.

GOETSCH, W. 1921. Regeneration u. Transplantation bei Planarien. Arch. f. Entwicklgsmech., xlix, 359.

1923. Tierische Chimären u. Künstliche Individualitäten. Naturwissenschaften, 327.

1923. Chimärenbildung bei Coelenteraten. Zoöl. Anzeiger, lvi, 289.

GOHRBANDT, E. 1926. D. Hauthomoioplastik im Tierexperiment unter besondered Berücksichtigung der Parabiose. Arch. f. klin. Chirurgie, cxxxix, 471.

HADLEY, C. E. 1929. The compatibility of the skin of Rana pipiens and Rana clamitans as tested by transplantation. Journ. Exper. Zoöl., liv, 127.

HALSTED, W. S. 1909. Auto- and isotransplantation, in dogs, of the parathyroid glandules. Journ. Exper. Med., xi, 175.

HAMBURGER, F. 1901. Biologisches über d. Eiweisskörper d. Kuhmilch u. über Säuglingsernährung. Wiener klin. Wochenschr., xiv, 1202.

1902. Z. Frage d. Immunisierung gegen Eiweiss. Wien. klin. Wochenschr., xv, 1188.

1903. Arteigenheit u. Assimilation. Leipzig.

HAMBURGER, F. UND B. SPECK. 1904. Biol. Untersuchungen über Eiweissresorption von Darme aus. Wien. Klin. Wochenschr., xvii, 641.

HAMBURGER F. 1913. Über Verdauung u. Assimilation. Wien. klin. Wochenschr., xxvi, 1948.

HANSEMANN, V. D. 1916. Bemerkung über d. Beziehung d. Bastardierung z. Transplantation. Arch. f. Entwicklgsmech., xlii, 126.

HARDE, E. 1928. Observations sur les Greffes intracerebrales de tumeurs homologues et heterologues. Annales de l'Institut Pasteur, xlii, 1259.

HARMS, W. 1913. Überpflanzung v. Ovarien in e. fremde Art. II. Mitt. Versuche an Tritonen. Arch. f. Entwicklgsmech., xxxv, 748.

HARVEY, N. E. 1922. Studies on bioluminescence. XIV. The specificity of luciferin and luciferase. Journ. Gen. Physiol., iv, 285.

HARRISON, R. G. 1924. Some unexpected results of the heteroplastic transplantation of limbs. Proc. Nat. Acad. Science, x, 69.

1925. Heterotransplantation of the eye in Amblystoma. Anat. Record, xxxi, 299.

HEDIN, S. G. 1911. Über d. spezif. Hemmung d. Labwirkung u. über verschiedene Labenzyme. Zeitschr. f. physiol. Chemie, lxxiv, 242.

1909. Über Hemmung d. Labwirkung III. Zeitschr. f. Physiol. Chemie, lxiii, 143.

1912. D. Immunisierung gegen Kalbslab. Zeitschr. f. physiol. Chemie, lxxvii, 229.

HEIDELBERGER, M., W. F. GOEBEL AND O. T. AVERY. 1925. The soluble specific substance of a strain of Friedländer's bacillus. Journ. Exper. Med., xlii, 701.

HERMANNSDORFER, A. 1923. Exp. Nierenstudien an Parabiose u. Einzelratten. D. Zeitschr. f. Chir., clxxviii, 289.

HERTWIG, O. 1898. D. Zelle u. d. Gewebe. Jena.

HERTWIG, O. UND G. HERTWIG. 1923. Allg. Biol., Jena.

HESSELBERG, C. 1915. A comparison of autoplastic and homoioplastic transplantation of thyroid tissue in the guinea pig. Journ. Exper. Med., xxi, 164.

HESSELBERG, C. AND L. LOEB. 1918. Successive transplantations of thyroid tissue into the same host. Journ. Med. Res., xxxviii, 33.

HESSELBERG, C., W. KERWIN AND L. LOEB. 1918. Auto- and homoiotransplantation of the uterus in the guinea pig. Journ. Med. Res., xxxviii, 11.

HIRSZFELD, L. UND W. HALBER. 1928. Über gegenseitige Beziehungen gruppenspezif. Struckturen bei Menschen u. Tieren. Zeitschr. f. Immunitätsforschung, lix, 17.

HOLMAN, E. 1924. Proteinsensitization in iso-skin grafting. Surg., Gyn. and Obstet., xxxviii, 100.

HÖPFNER, E. 1903. Über Gefässnaht, Gefässtransplantation u. Replantation von amputierten Extremitäten. Arch. f. klin. Chirurgie, lxx, 417.

INGEBRIGSTEN, R. 1912. D. Bedeutung d. Isoagglutinine für d. Shicksal homoiotransplantierten Arterien. Münch. Med. Wochenschr., lix, 1475.

ISSAJEW, W. 1923–1924. Vererbungsstudien an tier. Chimären. Biol. Centralbl., xliii, 115.

JAEGER, G. 1876. Über d. Bedeutung d. Geschmacks u. Geruchsstoffes. Zeitschr. f. Wissensch. Zoöl., xxvii, 319.

JEHN, W. 1907. Beiträge z. Parabiose. Zeitschr. f. exper. Pathol. u. Therap., vi, 16.

JENSEN, P. 1896. Über individuelle physiol. Unterschiede zwischen Zellen d. gleichen Art. Pflüger's Arch., lxii, 172.

JENSEN, C. O. 1903. Experimentelle Untersuchungen über Krebs bei Mäusen. Centralbl. f. Bakt., xxxiv, 28.

JOEST, E. 1897. Transplantationsversuche an Lumbriciden. Arch. f. Entwicklgsmech., v, 419.

KAMMERER, P. 1913. Vererbung erzwungener Farbveränderungen (Salamandra maculata). Arch. f. Entwicklgsmech., xxxvi, 4.

KING, H. D. 1902. Observations and experiments on regeneration on Hydra viridis. Arch. f. Entwicklgsmech., xiii, 135.

KOLODZIEJSKI, Z. 1928. Untersuchungen über d. Beteiligung d. transplantierten Haut an d. Regeneration. Extrait d. bulletin de l'Académie polon. d. sciences et des lettres. Sérié B.

KOPPANYI, T. 1924. Experiments on whole spleen transplantation. Journ. Amer. Med. Assoc., lxxxiii, 1654.

KORNFELD, W. 1914. Abhängigkeit d. Metamorph. Kiemenrückbildung v. Gesamtorganismus d. Salamandra maculosa. Arch. f. Entwicklgsmech., xl, 369.

KORSCHELT, E. 1907. Regeneration und Transplantation. Jena.
1929. Zur Frage d. morphogenetischen Induktion nach Transplantation. Arch. f. Entwicklgsmech., cxvii, 1.

KRITSCHEWSKI, J. L. UND R. E. MESSICK. 1927. Über heterogene Komplementbindende Antikörper. Zeitschr. f. Immunitätsforsch., lii, 339.
1930. D. Gruppenspezif. Differenzierung d. menschl. Organe. V. Über d. Verhalten d. Forssmannschen Antigene zu d. Gruppenspezif. Antigenen d. Menschen u. über d. lipoid Natur derselben. Zeitschr. f. Immunitätsforschung., lxv, 405.

KRONENBERG, M. 1923. D. Individualität. D. Naturwissenschaften, Hft. 18, 325.

KUBANYI, A. 1924. Hauttransplantationsversuche auf Grundlage d. Isoagglutination. Arch. f. Klin. Chir., cxxix, 644.

KÜTTNER, H. 1924. Z. Frage d. Heterotransplantation. Zentralblatt f. Chirurgie, li, 19.

LAMBERT, R. A. AND F. M. HANES. 1911. The cultivation of tissue in plasma from alien species. Journ. Exper. Med., xiv, 129.

LANDSTEINER, K. 1901. Über Agglutinationserscheinungen normalen menschlichen Blutes. Wien klin. Wochenschr., xiv, 1132.

LANDSTEINER, K. AND J. VAN DER SCHEER. 1924. Serological examination of a species hybrid. I. On the inheritance of species—specific qualities. Journ. Immunol., ix, 213.
1924. Serological examination of a species hybrid. II. Tests with normal agglutinins. Journ. Immunol., ix, 221.
1925. On the antigens of red blood corpuscles. Journ. Exper. Med., xlii, 123.

LANDSTEINER, K., J. VAN DER SCHEER AND D. H. WITT. 1925. Group specific flocculation reactions with alcoholic extracts of human blood. Proc. Soc. Exper. Biol. and Med., xxii, 289.

LANDSTEINER, K. 1927. Über Komplexe Antigene. Klin. Wochenschr., vi, 103.

LANDSTEINER, K. AND J. VAN DER SCHEER. 1928. Serological differentiation of stereo-isomeres. Journ. Exper. Med., xlviii, 315.

LANDSTEINER, K. AND C. P. MILLER, JR. 1925. Serological studies on the blood of the primates. Journ. Exper. Med., xlii, 841.
1925. Serological studies on the blood of the primates. II. The bloodgroups in anthropoid apes. Journ. Exper. Med., xlii, 853.
1925. Serological studies on the blood of the primates. III. Distribution of serological factors related to human isoagglutinatogens in the blood of lower monkeys. Journ. Exper. Med., xlii, 863.

LANDSTEINER, K. 1928. Cell antigens and individual specificity. Journ. Immunol., xv, 585.

LEHMANN, W. UND H. TAMMANN. 1926. Z. Immunisat. Funktion d. retikuloendothelialen systems, xlv, 493.

LENART, G. UND J. KOENIG. 1928. Über d. Isoagglutinationsgehalt d. Gewebssaftes u. d. Beziehung z. Gewebstransplantation. Klin. Wochenschr., no. 12, 549.

LEWIS, W. H. 1904. Experimental studies on the development of the eye in amphibia. Amer. Journ. Anat., iii, 505.

1906–1908. On the origin and differentiation of the otic vesicle in amphibian embryos. Anat. Record, i, 141.

LEXER, E. 1919–1924. D. freien Transplantationen. I, II Teil, Stuttgart.

LIGNAC, G. O. E. UND G. A. KREUZWENDEDICH VON D. BORNE. 1928. Verimpfunge. Mäusesarcoms auf ungespeicherte und auf mit Trypanblau gespeicherte Mäuse. Krankenheitsforschung, vi, 265.

1929. Über heteroplastische Gewächsverpflanzung, insbesondere auf mit Trypanblau gespeicherte Mäuse. Krankheitsforschung, vii, 119.

LILLIE, F. R. 1913. Studies of fertilization. Journ. Exper. Zoöl., xiv, 575.

1916. The history of the fertilization problem. Science, xliii, (Jan. 14) 39.

1921. Studies of fertilization. VIII. On the measure of specificity in fertilization between two associated species of the sea urchin genus. Strongylocentrotus, Biol. Bull., xl, 1.

1919. Problems of fertilization. Univ. of Chicago Press.

LINDEMAN, V. F. 1929. Integumentary pigmentation in the frog, Rana pipiens during metamorphosis with especial reference to tail-skin histolysis. Physiol. Zoöl., ii, 255.

LITTLE, C. C. AND B. W. JOHNSON. 1922. The inheritance of susceptibility to implants of splenic tissue in mice. Proc. Soc. Exper. Biol. and Med., xix, 163.

LITTLE, C. C. 1920. Factors influencing the growth of a transplantable tumor in mice. Journ. Exper. Zoöl., xxxi, 307.

LITTLE, C. C. AND E. E. TYZZER. 1916. Further experimental studies on the inheritance and susceptibility to a transplantable tumor, etc. Journ. Med. Res., xxxiii, 393.

LOEB, L. 1904. Weitere Untersuchungen über Blutgerinnung. Hofmeister's Beiträge, v, 534.

1903. On the coagulation of blood in its relation to thrombosis and the formation of fibrinous exudate. Montreal Med. Journ., July 1.

1903. On the presence of specific coagulins in the tissues of vertebrates and invertebrates. Med. News, Aug. 1.

1907. Einige neuere Arbeiten über d. Blutgerinnung bei Wirbellosen u. bei Wirbeltieren. Biochem. Centralbl., vi, 1.

1926. Autotransplantation and homoiotransplantation of cartilage in the guinea pig. Amer. Journ. Pathol., ii, 111.

LOEB, L. AND J. S. HARTER. 1926. Heterotransplantation of cartilage and fat tissue and the reaction against heterotransplants in general. Amer. Journ. Pathol., ii, 521.

LOEB, L. 1926. Autotransplantation and homoiotransplantation of cartilage and bone in the rat. Amer. Journ. Pathol., ii, 315.

1926. Autotransplantation and homoiotransplantation of the thyroid gland in the rat. Amer. Journ. Pathol., ii, 301.

1926. Further observations on autotransplantation and homoiotransplantation of thyroid gland in the guinea pig. Amer. Journ. Pathol., ii, 99.

1926. The individuality differential and the reactions against transplanted tissues and tumors with particular reference to the lymphocytic reaction. Journ. Cancer Res., x, 252.

LOEB, L. AND S. WRIGHT. 1927. Transplantation and individuality differentials in inbred families of guinea pigs. Amer. Journ. Pathol., iii, 251.

LOEB, L. AND H. D. KING. 1927. I. Transplantation and individuality differential in strains of inbred rats. Amer. Journ. Pathol., iii, 143.

LOEB, L. AND W. H. F. ADDISON. 1909. II. Transplantation d. Haut d. Meerschweinschens in Tiere verschiedener Species. Arch. f. Entwicklgsmech., xxvii, 73.

1911. Beiträge z. Analyse d. Gewebewachstums. V. Über d. Transplantation d. Taubenhaut in d. Taube u. in andere Tierarten. Arch. f. Entwicklgsmech., xxxii, 44.

LOEB, L. 1907. Beitr. z. Analyse d. Gewebewachstums. I. Über Transplantation regenerierenden Epithels u. über Serientransplantation von Epithel. Arch. f. Entwicklgsmech., xxiv, 638.

1920. The individuality-differential and its mode of inheritance. Amer. Naturalist, liv, 55.

1920. On the reaction of tissues towards syngenesio-, homoio- and heterotoxins and on the power of tissues to discern between different degrees of family relationship. Amer. Naturalist, liv, 45.

1921. Transplantation and individuality. Biol. Bull., xl, 143.

1918. An analysis of the behavior of organs after transplantation in the rat and of the power of resistance of the constituents of various organs. Journ. Med. Res., xxxix, 189.

1920. On differences in the results of various kinds of syngenesioplastic transplantations in dependence upon the relationship between donor and host. Journ. Med. Res., xli, 305.

1920–1921. Heterotransplantation of kidney. Journ. Med. Res., xlii, 1317.

1920. Heterotransplantation of the thyroid gland. Journ. Exper. Med., xxxi, 765.

1921. An analysis of factors which determine the life and growth of transplanted tissues. Proc. Soc. Exper. Biol. and Med., xvii, 153.

LOEB, L. AND M. S. FLEISHER. 1916. Transplantation of benign tumor. Journ. Cancer Res., i, 427.

LOEB, L. 1917. Tissue growth and tumor growth. Journ. Cancer Res., ii, 135.

1915. The influence of changes in the chemical environment on the life and growth of tissue. Journ. Amer. Med. Assoc., lxiv, 726.

1918. The organization of bloodclots after auto-, homoio- and heterotransplantation. Journ. Med. Res., xxxii, 353.

1918. The grafting of tissues into nearly related individuals in the rat and mode of inheritance of individuality differentials. Journ. Med. Res., xxxiii, 393.

1927. Syngenesiotransplantation in the rat. Amer. Journ. Path., iii, 45.

1927. Syngenesiotransplantation in the guinea pig. Amer. Journ. Path., iii, 29.

1926. Transplantation and potential immortality of mammalian tissues. Journ. Gen. Physiol., viii, 417.

1918. Syngenesioplastic transplantation of the thyroid in the guinea pig. Journ. Med. Res., xxxix, 39.
1917. Tissue transplantation and anaphylaxis. Journ. Immunology, ii, 557.
1918. Multiple transplantations of the thyroid and the lymphocytic reaction. Journ. Med. Res., xxxix, 71.
1917. Further investigations on auto- and homoioplastic transplantation of kidney tissue. Journ. Med. Res., xxxvii, 229.
1908. Tumor growth and tissue growth. Proc. Amer. Phil. Soc., xlvii, 3.

LOEB, L. AND M. S. FLEISHER. 1912. Untersuchungen über d. Vererbung der d. Tumorwachstum bestimmender Faktoren. Centralbl. f. Bakt., lxvii, 136.

LOEB, L. AND W. H. F. ADDISON. 1909. Beiträge z. Analyse d. Gewebewachstums. II. Transplantation d. Haut d. Meerschweinchens in Tiere verschiedener Species. Arch. f. Entwicklgsmech., xxvii, 73.

LOEB, L. 1911. Beiträge z. Analyse Gewebewachstums. IV. Über d. Einfluss v. Kombinationsreizen auf d. Wachstum d. transplantierten Uterus d. Meerschweinchen. Arch. f. Entwicklgsmech., xxxi, 456.

LOEB, L. AND W. H. F. ADDISON. 1911. Beitr. z. Analyse d. Gewebewachstums. V. Über d. Transplantation d. Taubenhaut in d. Taube u. in andere Tierarten. Arch. f. Entwicklgsmech., xxxii, 44.

LOEB, L., M. S. FLEISHER AND L. TUTTLE. 1922. The interaction between blood serum and tissue extract in the coagulation of the blood. I. Journ. Biol. Chem. li, 461.
1922. II. Journ. Biol. Chem., li, 485.

LOEB, L. AND S. LEOPOLD. 1907. On the difference in the results obtained after inoculation of tumors into the individual in which the tumor had developed spontaneously and into other individuals of the same species. Journ. Med. Res., xvii, 299.

LOEB, L. 1902. Further investigations in transplantation of tumors. Journ. Med. Res., viii, 44.
1903. Über Transplantation v. Tumoren. Virchow's Arch., clxxii, 345.
1902. On transplantation of tumors. Journ. Med. Res., vi, 28.
1902. Über Transplantationen e. Sarcoms d. Thyreoiden bei e. Weissen Ratte. Virchow's Arch., clxvii, 175.
1897. Über Transplantation von weisser Haut auf einer Defekt in schwarzer Haut und umbekehrt am Ohr d. Meerschweinchen. Arch. f. Entwicklgsmech., vi, 1.

LOEB, J. 1908. Über d. Natur. d. Bastardlarven zwischen d. Echinodermenei Strongylocentrotus franciscanus u. Molluskensamen (Chorostoma funebr.). Arch. f. Entwicklgsmech., xxvi, 476.

LOEPER, M. ET R. TURPIN. 1924. Lymphocyte et cancer. Review Critique. Annales de Medecine, xvi, 236.

LÖHNER, L. 1923. Über individualstoffe u. biochem. Individualspezifizität. Pflüger's Arch., cii, 490.
1921. Über menschl. Individual u. Regionalgerüche. Pflüger's Arch., cii, 25.

LUCKÉ, B., M. MCCUTCHEON, M. STRUMIA AND S. MUDD. 1929. On the mechanism of opsonin and bacteriotropin action. II. Journ. Exper. Med., xlix, 797.

LUMSDEN, T. 1929. Tumor immunity. Journ. Pathol. and Bacteriol., xxxii, 185.

1927. On the nature of immunity to implanted malignant tumors. Lancet, 116.

MANGOLD, O. 1923–1924. Transplantationsversuche z. Frage d. Spezifizität in d. Bildung d. Keimblätter. Arch. f. Entwicklgsmech., c, 198.

MANLEY, O. T. AND D. MARINE. 1916–1917. Influence of age on the permanence of subcutaneous autografts of the spleen in rabbits. Proc. Soc. Exp. Biol. and Med., xiv, 123.

1916. The transplantation of ductless glands with reference to permanence and function. Journ. Amer. Med. Assoc., lxvii, 26.

MARINE, D. AND O. T. MANLEY. 1920. Homoiotransplantation and autotransplantation of the spleen in rabbits. Journ. Exper. Med., xxxii, 113.

MARCHAND, F. 1901. D. Process d. Wundheilung mit Einschluss d. Transplantation. Stuttgart.

MASSON, J. C. 1918. Skin grafting. Journ. Amer. Med. Assoc., lxx, 1581.

MATSUAYAMA, R. 1921. Exper. Untersuchungen mit Rattenparabiosen. Frankf. Zeitsch. f. Pathol., xxv, 97.

MAY, R. M. 1923–1924. Skin grafts in the lizard. Brit. Journ. Exper. Biol., i, 539.

MAYEDA, T. 1921. Untersuchungen über Parabiose mit besond. Berücksichtigung d. Transpl. u. Hypernephrektomie. D. Zeitschr. f. Chir., clxvii, 295.

MORPURGO, B. 1928. Über d. Einfluss verschied. äusserer Faktoren auf d. Haftung von nicht autoplast. Transplantation. Verhandl. d. Pathol. Gesellschaft, 330.

1909. Über Parabiose bei weissen Ratten. Verh. d. deutsch. pathol., Gesellschaft, xiii, 150.

1926. Untersuchungen über d. individ. Konstitution an Parabioseratten. Frankf. Zeitschr. f. Pathol., xxxiv, 337.

1923. Nervenvereinigung an Parabioseratten. Klin. Wochenschr., 129.

MURPHY, J. B. 1926. The lymphocyte in resistance to tissue grafting, malignant disease, and tuberculous infection. Monographs of the Rockefeller Institute for Med. Research, no. 21.

1912. Transplantability of malignant tumors to the embryos of a foreign species. Journ. Amer. Med. Assoc., lix, 874.

1914. Factors in resistance to heteroplastic tissue grafting. Studies in tissue specificity. III. Journ. Exp. Med., xix, 513.

1916. The effect of adult chicken organ grafts on the chick embryo. Journ. Exper. Med., xxiv, 1.

1914. Studies in tissue specificity. II. The ultimate fate of mammalian tissues implanted in the chick embryo. Journ. Exper. Med., xix, 181.

1913. Transplantability of tissues to the embryo of foreign species. Its bearing on questions of tissue specificity and tumor immunity. Journ. Exper. Med., xvii, 482.

MURPHY, J. B. AND E. STURM. 1923. Conditions determining the transplantability of tissues in the brain. Journ. Exper. Med., xxxviii, 183.

MYER, M. H. 1913. Contributions to the analysis of tissue growth. XI. Autoplastic and homoioplastic transplantation of kidney tissue. Arch. f. Entwicklgsmech., xxxviii, 1.

NÄGELI, V. C. 1884. Mechanisch-physiol. Theorie d. Abstammungslehre. München.

NIEKAU, B. UND L. DUSCHL. 1925. Haematol. u. pathol.-anat. Untersuchungen an parabios. Ratten. D. Zeitschr. f. Chir., xci, 221.

NISSEN, R. 1923. Pathol.-Anat. z. Parabiosevergiftung. Zeitschr. f. d. ges. exper. Med., xxxv, 251.

OSHIMA, T. 1914. Über d. Schiksal d. homoplastisch transplantierten Hautlappens beim Menschen. Arch. f. klin. Chirurgie, ciii, 440.

PERTHES, G. 1917. Ist homöplastische Hautverpflanzung unter Geschwistern der autotransplantation gleichwertig? Centralbl. f. Chirurgie, xliv, 426.

PEEBLES, F. 1900. Experiments in regeneration and in grafting of hydrozoa. Arch. f. Entwicklgsmech., x, 435.

RAND, H. W. 1924–1925. Inhibiting agencies in outgrowth and regeneration. Anat. Record, xxix, 98.

RAND, H. W. AND M. ELLIS. 1926. Inhibition of regeneration in two-headed or two-tailed planarians. Proc. Nat. Acad. Sciences, xii, 570.

RAND, H. W. AND E. BROWNE. 1926. Inhibition of regeneration in planarian by grafting. Proc. Nat. Acad. Sciences, xii, 575.

REHN, E. UND WAKABAYASHI. 1912. D. homoplast. Transpl. d. Intermediärknorpels im Tierexperiment. Arch. f. klin. Chirurgie, xcvii, 1.

RIBBERT, H. 1898. Über Transplantation v. Ovarien, Hoden u. Mamma. Arch. f. Entwicklgsmech., vii, 688.

1895. Beitr. z. Kompensat. Hypertrophie u. zur Regeneration. Arch. f. Entwicklgsmech., i, 69.

RICHTER, M. N. AND H. I. JAFFE. 1928. Regeneration of autoplastic lymphnode transplants. Journ. Exper. Med., xlvii, 977.

1928. The autoplastic transplantation of tissues into the bone marrow cavity. Journ. Exper. Med., v, 981.

ROHDE, C. 1925. Über Versuche z. Überwindung d. Anheilungsschwierigkeiten homoplast. Transplantation. Beitr. z. klin. Chir., cxxxiv, 111.

ROUS, P. 1910. An experimental comparison of transplanted tumors and a transplanted normal tissue capable of growth. Journ. Exper. Med., xii, 344.

RUSS, S. AND G. M. SCOTT. 1927. Cross immunity with rat tumors. Journ. Path. and Bact., xxx, 564.

SALE, L. 1913. Contributions to the analysis of tissue growth. VIII. Autoplastic and homeoplastic transplantation of pigmented skin in guinea pigs. Arch. f. Entwicklgsmech., xxxvii, 248.

SALTYKOW, S. 1900. Über Transplantation zusammengesetzter Teile. Arch. f. Entwicklgsmech., ix, 329.

SALZER, H. 1909. Z. Frage d. Schilddrüsentransplantation. Arch. f. Chir., lxxxix, 885.

SAMPSON, M. M. 1922. Isoagglutination and heteroagglutination of spermatozoa. Biol. Bull., xliii, 267.

SANTOS, F. V. 1929. Studies on transplantation in planaria. Biol. Bull., lvii, 188.

SAUERBRUCH, F. UND M. HEYDE. 1909. Weitere Mitteilungen über d. Parabiose b. Warmblütern mit Versuchen über Ileus u. Uraemie. Zeitschr. f. exper. Pathol. u. Therap., vi, 33.

SCHOENE, G. 1909. Vergl. Untersuchungen über d. Transplantation von Geschwülsten u. von normalen Geweben. Beitr. z. klin. Chir., lxi, 1.

1912. Über Transplantationsimmunität. Münch. Med. Wochenschr., lix, 457.

1912. D.heteroplastische,homoioplastische Transplantation. Berlin.

1908. Exper. Untersuchungen über d. Transplantation Körperfremder Gewebe. Verh. d. deutsch. Gesellschaft f. Chirurgie, xxxvii, 174.

1913. Über Farbenwechsel d. Haarkleides nach d. Hauttransplantation. Zeitschrift f. d. ges. Exper. Med., i, 444.

1916. Austausch normaler Gewebe zwischen blutsverwandten Individuen. Beitr. z. klin. Chir., xcix, 233.

SCHMIDT, G. 1922. Stand u. Ziele v. Parabioseforschung auf Grund eigener Untersuchungen. Deutsch. Zeitschr. f. Chir., clxxi, 141.

SECÉROV, S. 1912. Weitere Farbwecksel u. Hauttransplantations versuche an d. Bartgrundel. Arch. f. Entwicklgsmech., xxxiii, 716.

SEELIG, M. G. 1913. Contribution to the analysis of tissue growth. IX. Homoioplastic and autoplastic transplantation of unpigmented skin in guinea pigs, xxxvii, 259.

SHAWAN, H. K. 1919. The principle of bloodgrouping applied to skin-grafting. Amer. Journ. Med. Sci., clvii, 503.

STILLING, H. 1905. Über d. Ergebnis d. Transplantation v. Nebennierengewebe Beitr. z. pathol. Anat., xxxvii, 480.

SCHULZE, W. 1922. Parabiose. Klin. Wochenschr., no. 40, 41, pp. 2007–2052.

SCHULTZ, W. 1917–1918. Gleichlauf von Verpflanzung u. Kreuzung bei Froschlurchen. Arch. f. Entwicklgsmech., xliii, 361.

1913. Vorschläge z. Studium d. somat. Vererbung., d. Bastardunfruchtbarkeit u. d. blastogenen Insertion mit Hilfe d. Keimzellenverpflanzung. Arch. f. Entwicklgsmech., xxxvii, 285.

1915. Parallele v. Bastardierung u. Transplantation u. Rückschlüsse auf. d. Vererbung, besonders bei mendelnden u. Gechlechtscharacteren. Arch. f. Entwicklgsmech., xli, 120.

1910. Verpflanzungen d. Eierstöcke auf fremde Species, Varietäten u. Männchen. Arch. f. Entwicklgsmech., xxix, 79.

1912–1913. Bastardierung u. Transplantation I. Arch. f. Entwicklgsmech., xxxv, 484.

1913. Bastardierung u. Transplantation II. Arch. f. Entwicklgsmech., xxxvi, 353.

1913. Bastardierung u. Transplantation III. Arch. f. Entwicklgsmech., xxxvi, 265.

SHIRAI, Y. 1921. On the transplantation of the rat sarcoma in adult heterogeneous animals. Japan. Med. World, 1, no. 2, 14 (cited from WOGLOM —Cancer Review, 1929).

SIEBERT, W. J. 1928. Effect of graded degrees of heat upon cartilage on homoiotransplantation and heterotransplantation in guinea pig. Proc. Soc. Exper. Biol. and Med., xxvi, 238.

1928. Auto- and homoiotransplantation of thyroid gland into brain of guinea pig. Proc. Soc. Exper. Biol. and Med., xxvi, 236.

SPEMANN, H. 1921. D. Erzeugung tier. Chimären durch heteroplast. embryonale transplantation zwischen Triton cristatus u. taeniatus. Arch. f. Entwicklgsmech., xlviii, 533.

SPEMANN, H. AND H. MANGOLD. 1924. Über Induktion u. Embryonalanlagen durch Implantation artfremder organisatoren. Arch. f. Entwicklgsmech., c, 599.

SPEMANN, H. AND B. GEINITZ. 1927. Über Wirkung organisat. Fähigkeiten durch Verpflanzung in organisat. Umgebung. Arch. f. Entwicklgsmech., cix, 129.

STEINEKE, F. 1925. D. Bedeutung d. Serodiagnostik für d. Verwandtschaftsforschung. Naturwissenschaften, Heft 41, 853.

STEVENSON, H. N. 1917. Tumor immunity in the chickembryo. Journ. Cancer Res., v, 449.

1918. Growth of tumors in the chick embryo. Journ. Cancer Res., iii, 63.

STRONG, L. C. 1926. A genetic study of the growth of a transplantable tumor. Journ. Exper. Zoöl., xlv, 231.

STRONG, L. C. AND C. C. LITTLE. 1920. Tests for physiological differences in transplantable tumors. Proc. Soc. Exper. Biol. and Med., xviii, 45.

STRONG, L. C. 1926. The genetic basis of susceptibility to tissue transplants. Proc. National Acad. of Sciences, xii, 181.

TAKAKUSU, S. 1922. Beitr. z. Physiol. d. Drüsen Untersuchungen mit parabiotischen Kaninchen. Biochem. Zeitschr., cxxviii, 1.

TAUBE, E. 1921. Regeneration mit Beteiligung ortsfremder Haut bei Tritonen. Arch. f. Entwicklgsmech., xlix, 270.

1923. Über d. histol. Vorgänge bei d. Regeneration v. Tritonen mit Beteiligung ortsfremder Haut. Arch. f. Entwicklgsmech., xcviii, 98.

TENNENT, D. H. 1929. Activation of eggs of echinometra matthaei by sperms of the crinoids comatula pectinata and comatula purpurea. Carnegie Inst. Publ., no. 391, 105.

1912. The behavior of the chromosomes on cross-fertilized echinoid eggs. Journ. Morph., xxiii, 17.

TODD, C. 1913–1914. On the recognition of the individual by haemolytic methods. Journ. Genetics, iii, 123.

TODD, C. AND K. G. WHITE. 1910. On the recognition of the individual by haemolytic methods. Proc. Royal Soc., Ser. B., lxxxii, 416.

TSCHERNISCHOFF, A. 1914. Über Eierstockverpflanzungen speziell bei Säugetieren. Beiträge z. pathol. Anat., lix, 162.

TYZZER, E. E. 1916. Rôle of inflammation in the immunity of mice to transplanted tumors. Journ. Cancer Res., i, 117.

UHLENHUTH UND SEIFFERT. 1925. Krit. Übersicht über d. Grundlagen d. Immunität gegen transplantable Tumoren. Med. Klinik., no. 16, 576.

UHLENHUTH, E. 1913. D. synchrone Metamorphose transplantierter Salamanderaugen. Arch. f. Entwicklgsmech., xxxvi, 211.

1912. D. Transplantation d. Amphibienauges. Arch. f. Entwicklgsmech., xxxiii, 723.

ULLMANN, E. 1929. Dekortisation d. Hodens nach vorausgegangener beiderseitigem Steinachschem u. beiderseitigem Dopplerschen Verfahren. Wien. Med. Wochenschr., lxxix, 1227.

UNDERWOOD, H. L. 1914. Anaphylaxis following skin grafting for burns. Journ. Amer. Med. Assoc., lxiii, 775.

WEDD, B. H., A. C. MORSON AND S. RUSS. 1913–1914. On the immunity conferred upon mice by radium irradiated mouse carcinoma. Journ. Path. and Bact., xviii, 566.

WELLS, H. G. 1929. The chemical aspects of immunity. N. Y. Chemical Catalogue.

WEIGL, R. 1913. Über homöopl. u. heteropl. Hauttransplantation bei Amphibien mit besond. Berücksichtigung d. Metamorphose. Arch. f. Entwicklgsmech., xxxvi, 595.

WILDEGANS. 1922. Über d. histolog. Vorgänge bei d. Hautimplantation nach Braun. Arch. f. klin. Chir., cxx, 415.

WILLIAMSON, C. S. 1923. Some observations on the length of survival and function of homogeneous kidney transplants. Journ. Urology, x, 275.

WINKLER, F. 1910. Studien über Pigmentbildung II. Transplantationsversuche an pigmentierter Haut. Arch. f. Entwicklgsmech., xxix, 620.

WITEBSKY, E. UND K. OKABA. 1927. Über d. Nachweis v. Gruppenmerkmalen in d. Organen d. Menschen. Zeitschr. f. Immunitätsforschung, lii, 359.

1927. Isoagglutinin und gruppenspezif. Lipoide. Zeitschr. f. Immunitätsforschung, liv, 131.

WITEBSKY, E. 1929. D. serolog. Analyse v. Zellen. u. Geweben. D. Naturwissenschaften, xvii, 771.

WOGLOM, W. H. 1923. A critique of tumor resistance. Journ. Cancer Res., vii, 283.

1929. Immunity to transplantable tumors. Cancer Review, iv, 129.

WOODWARD, A. E. 1918. Studies on the physiological significance of certain precipitates from the egg secretions of Arbacia and Asterias. Journ. Exper. Zoöl., xxvi, 459.

ZACHERL, H. 1928. D. Funktion d. Keimdrüsen im Lichte d. Parabioseforschung. Krankheitsforschung, vi, 174.

ZANGEMEISTER, W. UND E. KRIEGER. 1928. Serologische Untersuchungen. Spezifische Reaktionen zwischen d. Neugeborenen u. den Eltern. Münch. Med. Wochenschr., lxxv, 1577.

ADRENAL INSUFFICIENCY AND RELATED CONSIDERATIONS

S. W. BRITTON

Department of Physiology, University of Virginia

Over eighty years ago the attention of physicians was first called by Addison to several cases of idiopathic anemia which he had recognized in his practice at Guy's Hospital, and which were associated with profoundly destructive changes in the adrenal glands (3). In his classical memoir published a few years after his (rather coldly-received) address, Addison remarked in preface that practically nothing was known of adrenal physiology. He nevertheless recognized that the "modern physiologist" was a moving entity even at that early date. Because of the markedly anemic condition of the patients observed, the theory that "these hitherto mysterious bodies—the supra-renal capsules—may be either directly or indirectly concerned in sanguification" was postulated (4).

Reflection that even in these days of ultra-specialized—it might be called high-powered—physiology, three-quarters of a century later, very little definite information of adrenal activity beyond that of adrenin secretion by one part of the gland has been acquired, is thus not very comforting. Aside from a brief argument on medullary activities, a current physiological text merely relates the adrenals to the sex organs (190). Monographs on the internal secretions have dwelt largely on adrenalin, in considering the adrenal glands, and paid but passing mention to the cortex. The few reviewers who have sallied forth have gone a pace or two only beyond their own experimental thresholds (255, 256, 225, 220)—possibly with an inkling that the atmosphere is rather murky farther afield.

Attempts to elucidate the function of the adrenals which have been made throughout many years by some of the most skilled operators and accredited investigators now appear, however, to be meeting with a modicum of success. The recent demonstration that a cortical extract can be prepared which is able to preserve the life of adrenalectomized animals apparently indefinitely (276) is of outstanding significance.

The development of a potent organ extract invariably signalizes an outburst of experimental work in the pertinent field, and it is perhaps fortunately so. Hope is thus engendered that adrenal physiology may soon be stripped of much of its hazy theory and form a well-founded part of the endocrinological scheme.

Observed apparently for the first time in the sixteenth century by Eustachius, by whom they were called *glandulae renibus incumbentes*, the adrenal glands were long considered of slight account. In 1628 Riolanus designated them *glandulae suprarenales* (221). Only the vaguest notions, not replaced even today by any boastful knowledge of adrenal function, prevailed thereafter until recent times. The predilection of certain primitive races for the adrenal fat of their enemies for use in metabolic and deficiency diseases may be mentioned as of passing suggestive interest (Garrison). For early work on the adrenals, the treatise of Biedl (23) should be consulted. It should also be said that in many cases papers which may by some be considered germane to the subject have necessarily been omitted from this discussion.

Morphological considerations. It seems unfortunate that the two terms, suprarenal and adrenal, should both have gained such wide currency. In practically all animals lower than primates the glands are correctly termed "adrenals." In man, indeed, "suprarenal" appears to be somewhat of a misnomer: at least "adrenal" is equally applicable, and it is considered the proper term by many anatomists. Commonly text-books of anatomy describe the glands as lying *in front of* or along the medial border of the upper part of the kidney (Gray, Morris). The left gland is sometimes found as low as the renal hilus. "Adrenal" is generally used in comparative anatomy, and it would on many counts appear to be the term of preference.

Interesting data regarding the early development of the adrenals in man have been added to our knowledge within the past few years. The glands are said to be distinctly marked off from the surrounding tissues, and the central region appears highly vascular, as early as in 12 mm. embryos (Wieman). According to Keene and Hewer (150) chromaphil bundles now begin to appear, but not until the 25 mm. stage is reached is the true and also the fetal cortex (boundary zone) well defined. During the last 10 weeks of embryonic life the fetal cortex degenerates progressively, although it still forms the bulk of the gland at birth. The comparatively large adrenals which are found in the human fetus are due in considerable measure, indeed, to the remarkable development of the fetal cortex.

Lipoid appears normally in the fetal and true cortex at 24 weeks, while adrenin is said to be found in the medulla much earlier—at 12 weeks. After 18 weeks, adrenin is present in considerable amounts in the medulla. At birth very large blood sinuses as well as an exceedingly rich nervous supply are observed in the medulla. Some cells in the medullary tissue are said to give lipoidal reactions at this time (Keene and Hewer). In the chick, indication of the presence of adrenalin in the gland is found as early as the eighth day of incubation (Lutz and Case).

The rate of growth of the adult cortex and the disappearance of the fetal cortex may be used as rough estimates of post-natal age, according to Honan (128). Evidence is given by Scammon (243) regarding the degeneration of the inner and middle layers of the cortex in post-natal life. Donaldson (75) has further reported that the relative volume occupied by the medullary tissue in the rat decreases from birth to puberty by about 35 per cent. The latter observer also found relatively less medullary tissue in female than in male rats.

The presence of adrenalin in the gland in direct contact with the finest nerve fibrils, and in the smallest veins, has been commented on by Tammann (282). This observer considered that the cortex and the medulla were provided with a separate system of (small) arterial blood vessels. For some time this really subsidiary arrangement has been known to be present; the greater part of the blood supplied to the gland comes first, however, into intimate relation with the cortical elements—at least in higher forms. In the bird and also in reptiles the very rich venous supply was identified many years ago.

Henderson (123) has called attention to a rich network of blood spaces between the columns of cells in the cortex, through which blood passes inward to very large sinuses in the medulla. Only one layer of endothelial cells separates the blood from the parenchymal tissue. Furthermore, direct entrance from many of the blood sinuses into the central veins has been observed. Attention has also been directed by Henderson to the presence of heavy longitudinal bundles of muscle disposed along the central (medullary) vein and its tributaries, and the absence of circular muscle fibers. Because of this arrangement, contraction of the muscle is said to result in dilatation of the central vein.

It was shown many years ago that the adrenals are probably the most highly vascularized glands in the body (Neuman), and that the normal blood flow (e.g., in the cat) may reach 7 cc. per gram of gland per minute. This may be increased—as may also the oxygen consumption—after

the administration of adrenalin. The vascular irrigation of the adrenals in dogs has been shown to be about 35 cc. per kilogram of animal per minute (136). Houssay considered the adrenal blood flow more closely related to surface area than to body weight.

Adrenal transplants. Knowledge that the adrenal glands were necessary for life naturally led to numerous attempts to transplant the organs (see Boinet; Strehl and Weiss). The first successful cases of such operations in animals were claimed by Busch, Leonard and Wright (38). These investigators used thirty dogs and rabbits in their experiments, although data are given for the latter animals only. Whereas grafts in the testis and thyroid proved negative, positive results were said to follow implantation into the kidney. It is stated that one graft persisted for 274 days, although the evidence for survival does not on the whole appear conclusive.

Pediculate grafts were found by von Haberer and Stoerk (113) to survive indefinitely in dogs and rabbits. Oldberg (211) also observed that "pseudo-pedicle-transplants" in the kidney adequately maintained life for long periods in several dogs. Auto-transplantations into the omentum and spleen were unsuccessful.

Experiments which were carried out by Jaffe and Plavska (146) appeared to be singularly successful. The gland was divided in halves and inserted into the abdominal musculature in rats, and numerous fragments of cortex were similarly placed in guinea pigs. Such transplants sustained the animals for many weeks after the remaining adrenal had been removed, in apparently good health Only four of sixty-seven rats died, and in these the transplants had degenerated. Two guinea pigs were still surviving at 40 days, and six at 60 days, after which time their tissues were examined. Particularly in the case of survival of the latter animals, which all workers agree are very difficult to keep alive after adrenal removal, this evidence is very suggestive.

Physiological and microscopical evidence that autoplastic transplants may survive for nearly 300 days in the abdominal wall of the rabbit has also been presented by Jaffe (145). Using Sandison's technique it was demonstrated by Hou (132) that transplanted cortical cells may live in a transparent chamber in the ear of a rabbit for 4 to 6 weeks, while the medullary cells degenerate much more quickly.

In adrenalectomized cats it was found by Zwemer (310) that cortical transplants maintained life for an average of 6 $\frac{1}{2}$ days. This was considered a prolongation of the normal life-span of such operated animals, but in the light of more recent work on much longer-surviving animals the experiments can hardly be considered positive.

Successful grafts of the adrenal gland in cases of Addison's disease have sometimes been indicated (Pybus; Leschke). That considerable difficulty naturally confronts one who attempts the interpretation of clinical findings in such cases is nevertheless readily admitted.

It appears therefore that under certain favorable conditions in some animals at least, adrenal transplantation may be effective. Further work on this aspect of the subject has been considered elsewhere (145).

Hypertrophy. Regarding the possibility of hypertrophy of the adrenal tissues under experimental conditions, a good deal of confusion has prevailed for many years. During pregnancy, and in certain deficiencies—avitaminosis, inanition and starvation—it is indicated by a considerable array of evidence that the glands are usually definitely enlarged. As long ago as 1888 Stilling (265) noted that excision of one adrenal in rabbits led to enlargement of the remaining gland.

Early investigative work by Elliott and Tuckett (84) also tended to show that following unilateral adrenalectomy in the rabbit, hypertrophy of the remaining gland may take place. In the guinea pig also there was an apparent overgrowth of the medulla, but not of the cortex. Compensatory hypertrophy was admitted, nevertheless, to be not easily produced. It was later claimed by Elliott (83) that the accessory cortical tissues as well as the remaining principal gland in the cat tended to show enlargement following unilateral adrenalectomy.

Carefully conducted experiments by Boycott and Kellaway (28) have not supported the findings of many previous investigators. These workers used a large number of rabbits, with well-planned controls in the same litters, and failed to secure definite evidence of hypertrophy in any case. They comment on the remarkable fact that in autopsies on cases of Addison's disease, parts of the adrenals which have escaped destruction show no signs of compensatory overgrowth. A review of the earlier literature is given by Boycott and Kellaway.

In contradiction of the latter workers' findings are those just presented by Kojima (158), who observed the effects of unilateral adrenal removal on the remaining gland in 77 rabbits. In as many as 86 per cent of the cases a noteworthy compensatory hypertrophy of the cortical tissue was established. There also appeared to be a close relationship between the time elapsing after the initial single adrenalectomy and the degree of hypertrophy of the remaining gland. The adrenals in 200 normal rabbits were used as controls in these experiments. The left gland, it may be said, was noticeably heavier than the right in about 80 per cent of all cases, the average of the excess being approximately 12 per cent.

A recent report by MacKay and MacKay (189) provides interesting reading. The increase in cortical tissue of one gland following removal of the contralateral organ in the rat amounted to over 90 per cent, and was due almost wholly to increase in size of the cells. The medullary tissue showed no accession in size or in the number of cells.

It would thus appear that at least in some types, e.g., the rat and possibly the guinea pig, normal physiological (compensatory) hypertrophy may take place under optimal conditions. In many cases it is also apparent that previous workers have failed to consider adequately the normal increase in size which is referable to growth, or such abnormal changes as hyperemia and congestion, which may readily occur following laparotomy and vitiate the results when size and weight apart from such pathological conditions are considered as the critical factors.

Accessory tissues. It is scarcely possible to affirm without doubt, except perhaps after the most exhaustive microscopical search, that any animal does not possess accessory cortico-adrenal tissues. Their fairly wide distribution in the body renders it easily possible that one or more small aggregations of cortex may be overlooked by even the most careful observers. When one animal in a large number of experiments continues to live far beyond the normal expectancy after adrenalectomy, it would appear an ordinary human reaction at first to credit oneself with a remarkable achievement: yet under the circumstances this is perhaps the least possibility. Nor is it likely that the animal itself is to be allowed credit because it fortuitously possesses a good "general resistance." From the previous experience of many observers in such cases, cold judgment must almost invariably assign extended survivals to the dispensatory functioning of supplementary cortical bodies.

In their series of fifty-six dogs Banting and Gairns (14) made very careful search for accessory cortical bodies, but found none present. Stewart and Rogoff (262a) have performed adrenalectomy operations on more than one hundred and twenty dogs, and careful microscopical search failed to reveal an accessory adrenal in any case. Later, however, Stewart (256) reported finding one accessory adrenal in one hundred and fifty dogs.

In cats, accessory cortical masses appear to be present in five to ten per cent of cases. Elliott in a short series of experiments reports the higher figure (83), while Rogoff and Stewart (262a) have found about six per cent with accessories in their cases. It seems that gross inspection only was practised by the latter investigators—a not infallible method, to say the least.

It is significantly stated by Jaffe (145) that accessories are not found frequently in the guinea pig, cat or dog, "probably because the animals do not survive bilateral adrenalectomy for a sufficiently long time to permit the microscopic rests to hypertrophy."

In a paper by Kojima (158) it is shown that in normal rabbits accessory cortical tissues may be detected in 70 per cent of cases, whereas in doubly adrenalectomized animals the incidence is astonishingly increased to 94 per cent. Gross accessories were noted after adrenalectomy by Baumann and Kurland (19) in about 90 per cent of rabbits.

In rats accessory adrenals are said to be present in 50 per cent or more of cases. On gross inspection in several hundred animals, however, Jaffe has reported (145) that in only about 8 per cent of cases are accessory tissues detectable. After adrenal removal the incidence is shown to rise to about 25 per cent. Guinea pigs appear to possess small amounts of cortical accessory tissue in about 4 per cent of cases only (23).

Unilateral adrenalectomy. Observations by some of the earliest investigators that removal of one adrenal results in death have long since been disproved. It is now well known that serious apparent results do not usually follow such an operation. If one considers only the evidence which has been presented recently by very careful workers, however, it appears that unilateral or incomplete adrenalectomy may leave an animal not inconsiderably impaired.

Rogoff and Stewart on several occasions observed that their cats failed to survive excision of one adrenal gland. In one case (236), the condition of the animal after unilateral adrenal removal was excellent, but imperfectly heated quarters were said to have brought about death. Another animal developed coma and died within a few days after removal of the left adrenal. Elsewhere (254) they have reported a high mortality after sub-total adrenalectomy; in these cases (cats) about $\frac{1}{10}$ to $\frac{1}{8}$ of one gland was usually left intact.

Banting and Gairns (14) observed two dogs with one adrenal removed and the medulla of the other cauterized, which lived in good condition for three months. At this time the animals were put on a high protein diet. Within a week, it is stated, both dogs showed typical symptoms of adrenalectomy, and death occurred in three to four days.

Swingle (271) found that death with typical symptoms of adrenal insufficiency followed unilateral removal of the gland in two animals (cats). A number of cats that were operated on by Kellaway and Cowell (151) died of adrenal insufficiency, although a good deal of the cortex had been left intact.

Further interesting cases in which animals with one adrenal intact manifested the usual symptoms of adrenal insufficiency and rapidly succumbed after being fed large amounts of desiccated thyroid gland are cited by Zwemer (310). It is possible, of course, in such unilaterally operated cases as has been instanced, that the remaining gland has been in an atrophied condition and thus has not been able to function adequately to maintain life.

It is undoubted that the adrenal bodies may be affected on one side only in many fatal cases of Addison's disease. In four of the original eleven cases which were described by Addison, indeed, unilateral lesions of the glands appeared responsible for the fatal outcome of the disease.

Changes in the blood and urine after unilateral adrenalectomy are usually negligible, according to Lucas (183), although considerable increase was found in the blood urea in one case which this worker reported.

That it should be possible to remove with impunity and with no effect on the organism as much as fifty per cent of one of the most important tissues in the body is *prima facie* hardly tenable. It is altogether likely that many functional deficiencies would become apparent on subjection of such animals to rigid investigation, although the possibilities of rapid compensatory development and functional activity of the remaining adrenal tissue may amply suffice for the quiet routine of laboratory life. In this connection it may be well to mention, however, that the increasing number of tentative unilateral adrenalectomies which are being carried out on man for various diseases do not appear to have any present scientific or even clinical justification. A recent strong critique by Rogoff (224) offers a word in season on this matter.

Survival after adrenalectomy. The post-operative survival time of completely adrenalectomized animals is stated by many workers (266, 84, 201, 310) to be notably prolonged if a sufficient recovery interval is allowed to elapse between the first and second operations. The rather brief periods of survival which were observed by most of the earlier investigators, in part due to operative difficulties, indicate that definite conclusions should not be drawn from their results.

Recently Banting and Gairns (14) have indicated that dogs operated on in two stages survive for much longer periods than those in which the adrenals are excised at one sitting. The single operation has nothing in its favor and much against it, according to Rogoff and Stewart, whose word carries with it the weight of well-seasoned investigations on the adrenal bodies.

It should be borne in mind that in the dog the operation is more difficult than in most laboratory animals. In this animal, indeed, complete adrenalectomy at one sitting is a serious operation apart from the consideration of the highly important tissues which are extirpated.

Many of the earliest workers considered that death following adrenal removal might really be referable to damage of important structures during operation, and to shock and secondary infections. In the case of animals (dogs, cats) on which the two-stage operation has been carried out with highly improved present-day facilities, it is not mere charity to suppose that the many early deaths which have resulted have attested, probably *not* so much to faulty technique as has been urged many times by Rogoff and Stewart, but to the inability of the animal mechanism rendered doubly delicate by adrenalectomy to withstand even minor traumatisation of the tissues which are found in the vicinity of the adrenals. A number of Rogoff and Stewart's animals, it should be remembered, lived only a day or two after operation. It was not many years ago that Stewart himself stated, too, that "a *few* of the animals which die after removal of the adrenals no doubt. . . . succumb to accidental surgical consequences of the operation. . . . But there can be no doubt that in the vast majority of cases the animals die from adrenal insufficiency" (254).

In the cat or rabbit, bilateral removal of the glands takes about one-third of the time required for the same operation on the dog, and extracapsular trauma is relatively negligible. The observations by Corey (59) indicating that the survival periods following either the one- or the two-stage operation in the cat show no difference, can therefore be appreciated.

In a dozen one-stage operations recently carried out by the author on cats, an average length of survival of $7\frac{1}{3}$ days has been observed. This period is shorter than that found by Rogoff and Stewart, but somewhat better than the observations of other workers who allowed a recovery interval between removal of the right and left glands.

It is perhaps one of the most baffling facts to experimental physiologists today that all common laboratory animals from which the adrenal glands (and cortical accessory tissues when present) have been removed, whether by the single or two-stage operation, definitely die within a very short period. The complete operation can be conducted with very little trauma, in a comparatively short time—from 10 to 30 minutes in the case of most animals—and the tissue loss *per se* is extremely small—roughly one-three-thousandth of the body weight. The most skilful

surgical technique, combined with optimal post-operative attention, has not lessened the 100 per cent mortality which follows, usually within a week or ten days, complete removal of the adrenal tissues.

The controversy that ensued following the classical (although apparently not first-class) extirpation experiments of Brown-Séquard (37) lasted for a few years only, and for a considerable time thereafter (from about 1863 to 1879) no experimental evidence on this subject was published (23). A period then followed in which numerous attempts were made to produce the Addisonian syndrome by adrenal ablation. During the past twenty-five years, and particularly in the last decade, a formidable number of reports on adrenal function has been put into print.

Certain animals which were used by Brown-Séquard, it is now well recognized, appear to survive the operation indefinitely: but in these instances, adequate accessory adrenal tissues are undoubtedly present. From 50 to 80 per cent of white rats, and from 30 to 40 per cent of rabbits, which are adrenalectomized, have been found by various workers to live for at least many months in apparently normal health.

Lewis (177) has removed the adrenals in more than 400 rats, and observed a mortality varying from 20 to 40 per cent. Age and sex had no apparent influence on the results, and growth and reproductive functions were not interfered with following the operation. That certain deficiencies are present in adrenalectomized rats has nevertheless been frequently pointed out by Lewis and others.

Attention has been called by Jaffe (142) to the seriousness of the operation, for example, in the case of white rats. About 35 per cent of his animals (90) died within one month after adrenalectomy, and about 45 per cent survived for periods ranging up to seven months. The latter group gave evidence of a condition of chronic insufficiency, there being a progressive emaciation with marked or complete absence of fat, asthenia, and a lowered resistance to infection. In about 20 per cent of the cases there were no demonstrable clinical effects, and the animals appeared biologically normal in every respect. In this third group only were accessory cortical tissues observed macroscopically, and these were invariably large masses, sometimes even twice the size of the normal adrenal gland. Such an analysis by Jaffe demonstrates the exceeding importance of the adrenal mechanism from a new angle, and emphasizes the indispensability of a considerable amount of cortical tissue if normal bodily activities are to be adequately maintained.

Evans has recently made the observation (87) that all rats which are subjected to complete adrenalectomy fail to survive.[1]

Practically all guinea pigs die within a week or so after the adrenal operation. Stewart (254) has reported that in a series of 17 cases, 13 died in 6 days or less, and the 4 others lived 8, 11, 12 and 28 days respectively. No accessory cortical tissues were found in any case. Out of 10 cases which are cited by Gunn, Cori and Hartman (111) 3 died at operation and the others lived for 3, 3.5, 6, 7, 8, 9 and 26 days respectively.

In a recent series of 77 male rabbits which were operated on by Sataké and Kojima (242), a few which lived only a week to ten days showed no accessory cortical tissue. In those which survived longer, accessory tissue was invariably detected. About 40 per cent lived one year or longer. A rather close relationship existed, it was stated, between the duration of survival and the amount of cortical accessory tissue present. In a series of experiments which were carried out on 19 rabbits by Rogoff and Dominguez (226), 11 animals died within 2 weeks after operation, 3 lived into the third week, and 2 lived up to the fourth week. One animal lived 89 days, and two about 18 months.

It has been frequently stated that cats do not survive more than two or three days after complete removal of the adrenal glands. Over 15 years ago, however, Elliott (83) reported that in a series of 25 cats, 16 lived from 6 to 10 days after the (two-stage) operation. When both glands were removed in one operation, 17 animals died within 2 days, and 2 others died in 9 and 10 days respectively. In three animals which lived 22 days, 23 days and 9 weeks respectively, accessory cortical tissues were found. In contrast, a large number of reports which have been published within the past few years show no better results—in many cases they are poorer—than the foregoing.

One of the best series of experiments on cats is that reported by Rogoff and Stewart (236). In 46 adrenalectomized animals, they observed that the males survived 11 days and the females (non-pregnant) $10\frac{3}{4}$ days on the average, with the maximal survival period of $31\frac{1}{2}$ days. This is in rather striking contrast to their results of nearly ten years ago: at that time, 13 of their series of 18 cats died within 1 to 11 days after only subtotal (about 90 per cent) adrenal removal.

In reviewing a considerable body of evidence presented by numerous investigators, Biedl (23) showed several years ago that the maximal

[1] See paper by R. I. Pencharz, J. M. D. Olmsted and G. Giragossintz: Science, 1930, lxxii, 175.

survival period of adrenalectomized dogs was about 52 hours. Strehl and Weiss (266) observed survivals of five or six days in a few cases. Dogs which were operated on recently by Banting and Gairns (14) usually lasted only 3 to 5 days. Swingle (272) also kept six dogs alive, out of "about fifty" on which he operated, for 6, 7, 8, 9, 10 and 12 days respectively.

TABLE 1

Survival after adrenalectomy under various conditions (dogs). Data derived from a series of papers by Rogoff and Stewart on adrenal insufficiency

DATE OF PUBLICATION	BIBLIOGRAPHY NUMBER	SEX OF DOGS AND EXPERIMENTAL CONDITIONS	NUMBER OF ANIMALS	RANGE OF SURVIVAL AFTER ADRENALECTOMY	AVERAGE SURVIVAL PERIOD AFTER ADRENALECTOMY	NUMBER DIED UNDER 10 DAYS	PERCENTAGE OF DEATHS UNDER 10 DAYS
				days	*days*		
1925	261a	M. and F., controls	26	1.1–15.0	5.8	23	88.4
Nov. 1926	228	M. and F., controls	6*	1.2– 3.0	2.1	6	100.0
Nov. 1926	228	F., controls	39	1.5–11.5	6.4	33	84.6
Nov. 1926	228	M., controls	34	2.5–14.4	6.9	31	91.2
Apl. 1928	233	M. and F., controls	37	4.1–16.3	9.9	21	56.7
Apl. 1928	233	M. and F., dogs' adrenal extract, i.v.	28	5.7–27.7	11.9	13	46.4
Dec. 1929	262a	M., sheep's adrenal extract, i.v.	32	6.0–22.5	12.5	9	28.1
Dec. 1929	262a	M., sheep's adrenal extract, s.c.	19	4.7–23.2	10.4	10	52.6
Dec. 1929	262a	M., sheep's adrenal extract, orally	12	6.8–16.2	10.7	5	41.6
Aug. 1928	234	F., "in heat"	4	21.5–64.0	38.9	0	00.0
Jan. 1927	230	F., pregnant	17	1.3–58.1	22.1	4	23.5
Apl. 1928	232	M. and F., Ringer's, i.v.	17	3.0–53.7	19.6	4	23.5

* These short-lived animals were omitted by Rogoff and Stewart from their main series, although death from adrenal insufficiency was indicated by the autopsy findings.

The most noteworthy results on dogs have been achieved by Rogoff and Stewart, who have removed the adrenal glands from several hundred animals during the past ten years or more. Their survival figures offer a rather interesting study. The more significant ones in the various papers which they have presented have been gathered together and are reproduced in table 1.

It will be observed that in the first report (1925) on 26 adrenalectomized dogs, the average survival period was 5.8 days. In two larger series published a year or so later the averages were 6.4 days for 39 females, and 6.9 days for 34 males. About 18 months later still their average survival period increased to 9.9 days for 37 untreated male and female dogs. It will be observed, too, that not only has the *average* survival period increased, but the *range* of survival in days after adrenalectomy has also advanced from 1.1 to 15.0 in the 1925 report to 4.1 – 16.3 in the later investigation. More important even is the fact that only 11 per cent of the animals lived 10 days or over in the first series, whereas 43 per cent lasted 10 days or more in the series published about three years later. No explanation is offered by Rogoff and Stewart for the progressive and striking increase of life-span after operation which is shown by these *control* animals.

Improvement in the operative and post-operative technique developed by Rogoff and Stewart, and individual variation in animals, would appear to be the most likely factors involved. In one place, indeed, the frank confession is made that "our results have been so far superior to those reported by other investigators that we can explain them only by the extensive experience and practice which has enabled us to develop the necessary skill and technique for performing adrenalectomy properly" (225). After more than ten years admitted investment in the practice, it is creditable that their survival results on dogs and cats are approximately 100 per cent better than those obtained by most other investigators.

Adrenalectomy carried out on the goat by Moore and Purinton (207) did not result fatally in one case in 22 days. The animal was then sacrificed, and no accessory tissues were noticed at autopsy. Another goat lived into the eighth day after operation, but two kids survived only a few days.

A few workers have carried out adrenalectomy on monkeys. Kahn (148) observed that one animal, *Macacus rhesus*, lived four days in apparently normal health after excision of both glands in two stages. The animal ate well and was quite active during this period. On the fifth day, however, it showed weakness and refused food. Profound prostration quickly supervened, and the animal was chloroformed in order to make determinations for glycogen, of which only a trace was found in the liver. Stewart and Rogoff (259) have made observations on medulliadrenal function in a small number of monkeys (*macaques*).

Earlier experiments which were carried out on various lower animal

types have been reviewed at length elsewhere (291, 245). Birds are said to survive only a day or so after adrenalectomy (23). The extreme difficulty of the operation possibly accounts largely, however, for the reported results of experiments on such animals as pigeons. Fishes do not appear to withstand removal of the interrenal tissues, although the corpuscles of Stannius may be excised without prejudice to life (291). Frogs survive only a few days to a week or so after adrenalectomy (Loewi and Gettwert), although the very severe renal and vascular damage which cannot be avoided in carrying out the operation on amphibians must be in part responsible for the results obtained. Recent work on the toad (105, 106) shows that if the adrenal operation is thorough, all animals die within a few weeks with severe asthenic symptoms.

Beside the many factors which have been stated to shorten the life of adrenalectomized animals—operative shock and trauma, hemorrhage, cooling, etc.—it has been observed in this laboratory (34) that cats show symptoms more quickly when fed on a wholly protein diet. Milk-fed animals appear to live at least a few days longer. Banting and Gairns (14) have also noted that a protein diet with its consequent accumulation of protein-split products hastened death in their partially adrenalectomized dogs. The ingestion of liver by adrenalectomized cats was also observed by Hartman and his colleagues (120) to produce a marked increase in the blood urea and an exacerbation of the symptoms.

General symptoms of adrenal insufficiency. Description in intimate detail of the train of symptoms which are observed in animals deprived of their adrenal glands has been given by many investigators in recent years. It does not appear, however, that a great deal has been added to the evidence which was presented several years ago, and which has been summarized by many authors (145, 256, 270). Exhaustive treatment of the general symptomatology of adrenal insufficiency does not appear necessary here, and the observations will therefore be concerned more particularly with newer aspects of the subject.

The immediate recovery following removal of the adrenal glands in cats and dogs is not different from that after other well-conducted operations. If the experimental animal is not initially in vigorous health, or the operative technique is faulty or the anesthetization prolonged for an hour or so—for which there can hardly be any excuse—death will frequently result within a day or so. Usually the animal appears in fairly good health—sometimes in excellent condition—for

three or four days, or sometimes more than a week, after adrenalectomy. Careful nursing must be instituted, the quarters kept warm, and tempting food allowed if creditable survival periods are to be obtained. Even so, many animals develop an apathetic condition and succumb within a few days. In some of the papers published by Rogoff and Stewart it is admitted that several of their animals (dogs) have survived only one to three days. Banting and Gairns (14), who also adopted a very rigid operative and post-operative technique, lost a large number of their dogs within 50 hours after operation. And these experimenters are to be reckoned among the best who have contributed to our knowledge of the subject.

Dogs and cats which survive for a week or so after operation often appear normal on ordinary inspection; the wound heals well, food and drink are taken fairly readily, and activity may appear little less than usual until about two days before death. Rogoff and Stewart state that in the great majority of cases (and they have adrenalectomized many hundred dogs) their animals enjoyed "completely normal health" before the symptoms associated with adrenal insufficiency appeared. This represents, of course, their judgment based on general inspection only, and cannot be accepted as proof that the animals are in no way disabled.

From one to three days before death supervenes the ordinary portion of food is only partly eaten, and soon it is wholly refused, although tasty morsels may be accepted but with little relish for a short while. Occasionally anorexia and other terminal symptoms may appear more abruptly, (14), particularly in the dog. At this time slight muscular weakness develops, the hind limbs always being affected first, and vomiting and diarrhea may occur. Later muscular twitchings and convulsions are frequently but not invariably observed. The pulse becomes very slow and irregular, and body temperature falls a few degrees below normal.

Except perhaps when severe convulsive seizures are present—and they are more commonly only mild or moderate and not severe—it does not appear that painful sensations are experienced at any time by animals dying after removal of the adrenals. Usually there is a period of several hours when little interest is taken in the surroundings; gradually a more apathetic and a little later on an insentient condition sets in, which may again last for a few hours before death finally ensues.

While the foregoing symptoms of adrenal insufficiency are referable to cats and dogs, many of the conditions are also observed in other domesticated types, in rabbits, guinea pigs and albino rats, as well as

in wild species, e.g., the ground-hog (*Arctomys monax*) and the opossum (*Didelphys virginiana*) (34). Strehl and Weiss (266) found that the weasel and hedgehog also lived only a short while after adrenalectomy. The length of survival may modify the severity and occurrence of the symptoms. Many rats and rabbits which live for long periods after adrenal deprivation show a slowly progressive emaciation and often die from intercurrent infections. Noteworthy alterations in respiratory exchange are said frequently to follow the operation on rabbits (197).

It may be again noted that a number of cats show a notably diminished relish for the ordinary meat diet after operation, although milk and fish foods may be taken readily. Asthenia is observed concurrently with anorexia, and may persist for several days before convulsions and death eventually take place.

According to the writer's experience with many different animal types—dogs, cats, rabbits, guinea pigs, ground hogs, opossums and frogs—the general symptoms of adrenal insufficiency appear to follow a fairly similar course in all species. The limited terminal symptoms which are presented also by adrenalectomized birds apparently do not differ from those observed in other types.

Circulatory changes. Several years ago Elliott (83) made observations on the outstanding changes produced in cats following adrenal removal. An almost complete paralysis of the vasomotor mechanism and of the cardio-acceleratory nerves was noted, although other nerves responded normally to excitation. These changes were considered due to the abolition of adrenin secretion, since injected adrenalin brought about a rise in arterial pressure and acceleration of the heart. Electrocardiograms which were taken by Sir Thomas Lewis from one of Elliott's cats, surviving two weeks after operation, showed no variation from the normal.

Hoskins (130) has considered at length the relation of the adrenals to the circulation, and has reached the conclusion that the collapse of the circulatory mechanism following adrenalectomy is proof of a definite functional interrelationship. That some product of the adrenal tissues —medullary or cortical—is necessary for maintaining normal sympathetic nerve activities on the blood vessels has been deduced by Coombs (58) from her experiments. Both the pulse rate and the cardiac minute output were found by Harrison and his associates to be regulated in part at least by the adrenal glands.

The average level of the arterial pressure in adrenalectomized rats is said by Durrant (80) to be only 77 mm. Hg, with a range of 52 to 95

mm., in contrast to an average of 111 mm. and a range of 45–135 mm. for normal animals. Decapsulated dogs are said by Biasotti (22) to show a progressive fall of arterial pressure when death occurs in two or three days, whereas longer-living animals show an initial fall to a subsequent persistently low level.

The experiments of Rogoff and Dominguez (227) on dogs have been widely quoted. These investigators conclude from their results that a fall in arterial pressure occurs in adrenalectomized animals only a few days before death. If their two experiments are analyzed, however, it will be seen that in one case no regular or consistent readings were obtained, and that the second case should be given quite a different interpretation from that given by Rogoff and Dominguez. Whereas on the day of the adrenal operation the arterial pressure was 170 mm. Hg, it fell to 140 mm. 4 days later, to 110 mm. at 6 days, to 98 at 7 days, to 89 at 10 days, and to 77 mm. at 11 days. The next day the animal was found dead. The same experimenters used rabbits in their earlier work (226), and the results on these animals as well as the above must be considered at best equivocal.

It has been commonly observed that the blood becomes much darker in color, flows very sluggishly, and is markedly concentrated in animals which have been subjected to adrenalectomy. Many years ago it was shown by Gradinescu (108) that a steady rise in the number of red blood corpuscles per cubic millimeter could be detected in his operated animals. This investigator considered that a change in permeability of the blood vessel walls resulted in an escape of plasma to the tissues. Numerous authors have since emphasized the condition noted by Gradinescu and have advanced various interpretations for the phenomenon.

Dale (74) considered that the increase in blood concentration was associated with an increased susceptibility to histamine which followed adrenal ablation. A cortical defect was assumed by Kellaway and Cowell (151) to be responsible for the increased blood concentration. These observers did not support the theory of Gradinescu that loss of plasma from the blood took place; they noted that there were no collections of fluid in the serous spaces, and that the tissues always appeared dryer than usual. Joelson and Shorr (147) found that the blood concentration usually but not invariably increased after adrenalectomy.

The corpuscular content may increase from about fifty to sixty per cent, while the plasma correspondingly decreases, according to Lucas (183). The increase in concentration begins soon after operation, and is very rapid in animals surviving only short periods, and more gradual in

instances of long survival. It is often found impossible, indeed, to secure 0.1 cc. blood from the superficial vessels of smaller laboratory animals (e.g., cats) a few days before death occurs (34)—a condition which may be considered referable, of course, to the cardiovascular asthenia of adrenal insufficiency.

According to Rogoff and Stewart the anhydremic condition may occur in dogs during the period of "good health" which follows the operation. These workers found in some cases of severe adrenal insufficiency that the red blood cell count in dogs rose to 10,000,000 per c.mm., while the specific gravity of the blood increased to about 1070. Nevertheless, in one case no change in blood concentration occurred up to one and a half days preceding death of the animal.

Swingle among others has also called attention to the concentration of the blood in his operated animals (271), and considers it accounts for the rise in protein and total nitrogen.

It is well to observe that even normal dogs which have been fasted for a few days, with plenty of water available, show considerable increases in blood concentration—from over 9 per cent in three days to approximately 11 per cent in five days (Barbour and Hamilton). It thus appears only reasonable to expect that a rather definite concentration of the blood would be observed in such a severe bodily disturbance as that of adrenal insufficiency, in which condition fluid as well as solid foods are often refused for two or three days before death supervenes. Changes in blood concentration have moreover been noted under a variety of circumstances, e.g., after the injection of adrenalin (171) or of insulin (77), and also following intestinal obstruction (94).

Zwemer and Lyons (311) have investigated the leucocyte changes after adrenal removal in the cat. A decrease in the percentage of polymorphonuclear neutrophiles and increase in lymphocytes generally occurred in long-surviving animals. Observations on the relationship of the adrenal glands to anoxemic polycythemia have been presented by Izquierdo (140).

Blood chemistry after adrenal removal. Marshall and Davis called attention several years ago (201) to the increase in blood urea after adrenalectomy to about twice the normal amount; they observed that it remained high until just before death, when it rose still higher. The cause of this increase was considered to be the reduction of kidney function, since injected urea and creatinine were excreted very slowly. It was thought possible that some substance secreted by the adrenals might be necessary for kidney function.

Since these observations, Lucas (183) has shown that in dogs the non-protein and urea nitrogen in the blood increases after adrenalectomy up to three or four times the normal amount; but this is interpreted as representing a terminal stage phenomenon. Only a small number of observations are reported by Lucas, and it is to be remembered, too, that the survival periods of his animals were in many cases very short—much shorter than those of Rogoff and Stewart. Considerably higher figures for the urea and non-protein nitrogen are given by the latter workers for their longer-surviving animals. They observed that in eight cases in which analyses were carried out over several days on the blood of adrenalectomized dogs, the urea and non-protein nitrogen usually rose progressively for five or six days preceding the death of the animal. The increases were often noted to precede even the appearance of serious symptoms, and they apparently heralded the approaching dissolution. In two cases of long-surviving adrenalectomized pregnant animals, in which determinations were able to be made over more protracted periods, the non-protein and urea nitrogen showed considerable increases for over two weeks or so before death occurred. An augmentation of the urea nitrogen is the great factor concerned in the increase of non-protein nitrogen, but the "undetermined fraction" also may increase considerably.

That the nitrogen increases tend to parallel the severity of the symptoms of adrenal insufficiency has been emphasized by Wyman and Walker (308). Animals (rats) which showed no noteworthy changes were found later to possess gross accessory cortical tissues. Furthermore, successful cortical transplants, in the absence of demonstrable chromaffin tissue, prevented the increases in non-protein and urea nitrogen.

Renal damage may possibly account for the accumulation of urea and non-protein nitrogen, in the opinion of Lucas, although urinalyses indicate that nitrogenous and inorganic waste materials are excreted even up to the last stages preceding death. The amounts present in the blood at the time of death were not considered as lethal, since markedly higher figures were noted after ureteral ligation.

Slight diminutions in urinary output of urea and total nitrogen were found in rabbits operated on by Kojima (158). Swingle has also drawn attention to the decrease in urinary output in several cases.

That the percentage of blood chlorides in adrenalectomized dogs is decidedly decreased was found by Lucas. Moderate diminution in blood chlorides has been observed too by Rogoff and Stewart (229).

In operated cats the plasma solids appear to be uniformly increased from 8 to 10 per cent, while the plasma sodium and chlorine are said to be decreased to the extent of 15 and 9 per cent respectively, according to Baumann and Kurland (19). These workers also obtained rises of plasma potassium and magnesium, and occasionally of calcium, in their operated animals. The lowering of sodium and chlorine in the blood was considered, however, to be one of the most important derangements.

Swingle and Eisenman (273) have consistently noted diminutions in pH, CO_2 tension, serum bicarbonate and total acid in the blood of adrenalectomized cats. It was considered at one time by Swingle that the uncompensated acidosis which occurred was due to failure of the kidneys adequately to eliminate acids, and was similar to the condition found in certain types of nephritis. Later (271) Swingle concluded that the cause was extra-renal in origin. The early symptoms of adrenalectomy, anorexia and lassitude, may be due it was suggested to an initial decline in alkaline reserve and blood sugar.

Yonkman (309) has called attention to similar conditions of acidosis and decrease in blood pH in his operated dogs. The glycemic percentage fell, he observed, with the onset of symptoms and the initial fall in CO_2 capacity.

The calcium content of the blood serum has moreover been found to be increased at the time of, or sometimes before, the development of serious symptoms of adrenal insufficiency in dogs by Rogoff and Stewart (229, 235), and in cats by Hartman and his associates (120). Hypercalcemia in a few cases (dogs) up to 40 per cent above normal was observed by Taylor and Caven (283). It seems altogether likely, however, that this increase and also other variations in the inorganic constituents of the blood may easily be accounted for by the increased concentration of the blood which takes place after adrenal excision, as Lucas and others have suggested.

For many years the influence of the adrenal glands on cholesterol metabolism formed the subject of considerable controversy. Recent investigations do not lend support to many of the older experiments, although the high cholesterol content of the cortex is undoubted. Among many others, Baumann and Holly (18) have demonstrated, for example, that bilateral adrenalectomy produces only negligible variations in blood cholesterol. Lucas has further observed no appreciable effect on the ratio of cholesterol ester to free cholesterol, and concludes that the adrenals have practically no function in connection with cholesterol metabolism. In their long-surviving animals Rogoff and Stewart also obtained results which were likewise negative.

It is not possible, of course, that the small (absolute) amount of cholesterol which is found in the adrenal cortex could constitute a reservoir of this substance for the whole body, and the secretory theory also appears untenable. Chamberlain (53) has recently again stressed the great variations in cholesterol content of the adrenals, however, and reverted to their probable active relationship to "cholesterol physiology." Some experiments which he reports in brief appear to suggest that cholesterol may be synthesized in the cortex. At different times, it may be mentioned, nearly every organ in the body has been suggested as possibly possessing a cholesterogenic function. A review of the recent literature and further experimental evidence may be consulted in the paper by Randles and Knudson (218).

Effects on carbohydrate metabolism. There is common agreement among all observers that carbohydrate metabolism is interfered with at least to some extent following adrenalectomy. A number of the older investigators found the blood sugar to be much reduced shortly after the operation, but in most cases their animals survived only a few days and the observations are thus of questionable value. One of the best reviewers has concluded from a large mass of data that the adrenal capsules affect in some way the formation and utilization of glycogen (23).

In more recent years Kuriyama (170) has made a number of observations on rats, and has found that animals without adrenal glands show a significant disability in storing glycogen when compared with normal animals. The blood sugar of the operated animals was also somewhat lower than normal. Kuriyama presents a good review of the older literature.

Artundo also has recorded notable diminutions in blood sugar, and also in hepatic and muscle glycogen, in bilaterally adrenalectomized rats. The changes did not appear to be constant, however, and possibly accessory cortical tissues played a part in the results. A diminution of glycogen in the liver for two weeks after adrenalectomy was also noted by Houssay and Artundo (133). Viale (288) has furthermore observed a reduced glycogen content of muscle following adrenal removal.

In a recent paper by Cori and Cori (62) it is reported that adrenalectomized rats and mice show an almost complete disappearance of liver glycogen when fasted for 24 hours, although the muscle glycogen is scarcely affected beyond that in similarly starved normal animals. A considerable fall in blood sugar correspondingly occurred in the operated rats.

A large number of blood sugar determinations have been made in rats before and after adrenalectomy by Wyman and Walker (308). Following operation and coincident with the appearance of symptoms the blood sugar values fell from the normal average of 82 mgm. to about 55 mgm., while in the terminal convulsive stages levels as low as 30 mgm. were reached. In rats which possessed gross accessory cortical tissue, or on which successful cortical transplants had been made, the blood sugar remained within normal limits. From the results it was suggested that the cortex is concerned in the steady maintenance of the blood sugar level.

Stewart and Rogoff considered from a few observations on rats and rabbits several years ago (258) that the formation and storage of glycogen in the liver was not affected by removal of both adrenals. Recognition within recent years that such animals are particularly well blessed with accessory tissues possibly explains in part some of the inconsistent findings and suggests that caution should be exercised in the interpretation of the results.

Hartman and his co-workers (120) observed that the blood sugar in cats began to fall a few days after the operation, and decreased markedly during the last few days of life. Swingle (270) also has discussed at length the serious diminutions in glycemia which he observed in adrenalectomized dogs and cats, and suggested that death may possibly be referable in part to hypoglycemia. A small amount of cortical tissue, he emphasizes, will suffice to keep animals alive with a normal blood sugar percentage.

The earliest symptom of adrenal insufficiency in dogs has been stated by Estrada (86) to be hypoglycemia, which occurs within a few hours after operation. Banting and Gairns (14) and also Rogoff and Stewart (228, 229) have considered that the fall in blood sugar is rather related to the terminal symptoms of adrenal insufficiency. The animals used by the former observers did not last sufficiently long after operation, it would appear, for reliable conclusions to be drawn from their findings. For a day or two after an animal has been subjected to operation under an anesthetic it is well known that a considerably enhanced blood sugar percentage is usually observed. The tables which are presented by Rogoff and Stewart show in important instances—when blood sugar determinations were made over relatively long periods—that significant diminutions from the normal glycemic level took place several days before death supervened.

In a paper just published by Lumley and Nice (184) it is observed

that not only is the blood sugar of adrenalectomized rats under quiet conditions notably lower than that of normal animals, but that on excitation (by induced shocks sufficient to cause struggling) no increases in the glycemic percentage are usually evoked. Instead, *diminutions* occurred in most of the operated cases, whereas increases up to 89 per cent took place in the normal cases. In previous work (32) it has also been found that decreases in blood sugar usually occur on exciting medulliadrenalectomized cats (the cortex being intact) by an aggressive dog. Lumley and Nice concluded that the adrenal glands play an important rôle in bringing about mobilization of carbohydrates in the body.

The reduction of sugar in the blood of adrenalectomized animals is particularly noteworthy in view of the fact that the blood at the same time becomes markedly concentrated and probably much reduced in volume. While even the observed change is considerable, there must be a very serious *absolute* depletion of circulating glucose. These considerations in conjunction with the diminution of hepatic glycogen reserves lend emphasis to the growing conception that the adrenals are especially concerned in carbohydrate metabolism.

Macleod and Pearce (191) reported some years ago that stimulation of the splanchnic nerves, or of the hepatic plexus, does not produce hyperglycemia in the absence of the adrenal glands. Pilocarpine injections (173), and the production of hemorrhage (281), are also ineffective or much less active in exciting glycogenolysis in adrenalectomized animals. Admission has been made by Stewart and Rogoff (260) that adrenal intervention is in some way linked up with hyperglycemia produced by morphine. One is here tempted to recall that the hyperglycemia which occurs on injecting adrenalin is now said (7) to have as an accompaniment a remarkable increase in blood alcohol; at greatest however—and that in the fowl—the hyperalcoholemia reaches merely 0.005 per cent!

In cases of interference with medulliadrenal function the extraordinary increase in sensitivity of animals to insulin has been discussed by many investigators. It was recently shown by Britton, Geiling and Calvery (35), by whom the subject is reviewed, that the complete suppression of adrenin secretion by evacuation of the medulla in cats resulted in a four- to ten-fold increase in sensitivity to insulin njection. Nevertheless, the hepatic glycogen reserves in such animals were maintained at practically normal levels. Evidently the mobilization of carbohydrates is seriously hampered in the absence of functioning adrenal medullary tissue.

Whether or not it is still possible after adrenalectomy to produce piqûre glycosuria has been a moot point for several years. Although negative results appear to have been far more frequent, under some conditions of carbohydrate balance in the body it does seem that positive proof has been forthcoming. This phase of the subject scarcely warrants discussion here, however, and the review and experimental evidence which have been presented by Fujii (92) need only be mentioned.

Much as one would take pleasure in entering into the subject of adrenal extracts and adrenalin effects on carbohydrate metabolism, and the consideration particularly of such recent important work as that of Cori and Cori (62, 64), and of the Harvard workers, these enjoyments must also be yielded to other reviewers. Ample evidence has been presented in the relatively small number of papers quoted here to justify the belief that the adrenal mechanism—the medulla certainly and probably also the cortex—is intimately involved in various phases of carbohydrate metabolism in the body. Perhaps specifically the important shifts that occur *via* the blood stream between the splanchnic and somatic depots, as well as oxidations in the muscular tissues, are governed largely through adrenal activities. Such broad statements can hardly give offence, although a great deal more might be said without serious conflict with others' concepts. It does nevertheless appear certain that the near future will bring a much better understanding of the matter.

The adrenals and general metabolism. Animals which have been subjected to adrenal extirpation are markedly handicapped in their ability to perform muscular exercise. The total work done by adrenalectomized rats before complete fatigue set in was shown by Gans and Miley (95), for example, to be only one-sixteenth of that carried out by control animals. Durrant (80) noted also that operated rats, although they appeared on ordinary observation to be just as active as controls, really were much less active according to revolving cage measurements. In lower types, e.g., the frog, a much greater tendency of muscle to fatigue after adrenalectomy has also been shown (Hirase).

That fatigue is produced according to the degree of adrenal insufficiency present has been maintained by Mira and Fontes (203). Stewart and Rogoff (257) have found a definite although not very great depletion of the adrenin store in the gland with nerves intact, compared to its denervated fellow, after severe muscular exertion has been carried out by cats and rats.

A good deal of evidence indicates that metabolic activities are diminished considerably after adrenal removal (Aub et al., Artundo, Houssay and Artundo, Gayda). Scott (296) and also Marine and Baumann observed, however, a rise in heat production following sublethal excision of the adrenal organs. The latter workers associated the phenomenon with an increased rate of thyroid secretion, since its suppression abolished or greatly lessened the increase in metabolism.

Many authors (177, 20, 51, 202) have shown that adrenalectomized animals are particularly sensitive to cold. A gradually decreasing susceptibility to temperature changes which occurs in some cases is ascribed to hypertrophy of accessory adrenal tissues. Various relationships of the adrenal glands, particularly the medulla, to low environmental temperatures have been called attention to elsewhere (31). The outstanding importance of the adrenal tissues in the chemical regulation of body temperature has also been recently emphasized and reviewed by Cannon and his co-workers (41, 48). Marked changes which take place in the glands during fever have been discussed at length by Cramer (70a).

A large body of evidence shows that adrenalectomized rats, although surviving in apparently normal health, are markedly hypersensitive to various toxic substances. To morphine injection operated animals appear particularly sensitive (179, 189), although Stewart and Rogoff considered from their results that this was not the case in rats.

Heightened sensitivity to various substances has been noted by Crivellari (nicotine, acetonitrile, histamine), and Molinelli (diphtheritic toxin). Numerous observers have recorded a lowered tolerance toward histamine injections following adrenal extirpation, and a test for cortical deficiency based on this relation has been suggested (Scott; Gottesman and Gottesman). Subcutaneous injections of adrenalin given twice daily for a week following adrenalectomy afford protection to rats, however, against lethal doses of histamine in 50 per cent of cases (214).

Gastro-intestinal and pathological changes. One of the first observations on gastric ulceration following adrenal removal was that of Gibelli in 1909 (100). The condition has frequently been alluded to since that date. In his early investigations, Elliott also noted that at autopsy ulcerated areas appeared in the gastric mucosa. Before death the gastric juice possessed its normal acidity, which was considered "a token of its full digestive power" (83).

In a preliminary article, Stewart and Rogoff (261a) showed that the more prominent symptoms of adrenalectomy pointed very strongly to

profound disorganization of the digestive system. Blood and bile were rather common findings in the vomitus and feces, in their experiments. In a recent article (262a) considerable emphasis has again been placed by these investigators on the pathological findings in the gastro-intestinal tract following adrenal removal. In 118 adrenalectomized dogs there were found gastric ulcerations in 48 cases, while in 89 similarly operated cats 29 showed ulcers. In "normal" cats, gastric ulceration was said to be rare.

Inquiry into the cause of gastric ulcer occurrence after adrenal excision has been made by Mann on dogs and cats. The ulcers appeared to develop during the moribund period, but only in an acid medium. Gastric juice was considered a secondary although a necessary factor in producing the necrotic areas.

Marked functional derangements were observed by Alvarez and his associates (5) to follow removal of the adrenal glands in rabbits. The normal peristaltic rushes were inhibited, the rate of the rhythmic contractions was slowed, and conduction along the bowel was impaired. The threshold for faradic stimulation was also lowered, and the latent period markedly shortened. These conditions were said to resemble the changes following splanchnicotomy. It was shown that after splanchnic nerve section or vagotomy, gastric ulcers often occurred.

It should be remembered that gastro-intestinal disturbances and ulcerations may be readily induced in animals by the administration of various toxic substances (264, 286). In numerous disease conditions it is also well known that necrosis of the gastric mucosa is of rather common occurrence, although it is often referable to terminal or post-mortem conditions.

Banting and Gairns (14) made careful analyses of the tissues of their animals (dogs) which died following adrenal removal. The most constant condition which they emphasized was general enlargement of the lymph glands, with wide-spread proliferation of the plasma cells and endothelial leucocytes. A considerable amount of albuminous material, and frequently red blood cells, were found in the markedly edematous nodes. These findings, with degeneration of the liver cords and nephrosis of the kidney, were considered strong indication of the accumulation of a toxic substance in the blood. Strikingly, there was found to be very little normal liver tissue left, since the necrosis was so extensive, in their longer-lived dogs.

Besides the very common occurrence of blood and congestion in the alimentary canal which has been noted at autopsy by Rogoff and Stew-

art (228, 233), these workers have stressed the more invariable finding of pancreatic hyperemia. In their dogs and cats, this condition was practically always very marked. Unpublished observations on adrenalectomized marmots which have been made in this laboratory are in accord with the foregoing. Animals which lasted throughout the winter without adrenal glands and perished in the spring showed extreme pancreatic disturbance: usually the gland was very shrunken and thin and congested in appearance, and on section showed hemorrhagic patches throughout, diffuse sclerosis and atrophy. In one long-surviving animal only a fine web of tissue not at all resembling pancreas was found at autopsy; microscopically this did prove, however, to be very atrophic pancreatic tissue.

In some of their longer-surviving dogs, Banting and Gairns observed that the pancreas showed considerable congestion. Noteworthy hyperemia of the stomach, liver, spleen, and particularly of the pancreas has been recorded by Estrada (85) in dogs which survived up to nearly six days.

MacMahon and Zwemer (192) have remarked on the congestion of the liver in adrenalectomized cats, but have placed emphasis on the marked lymphoid hyperplasia and fatty degeneration of the kidney tubules which they observed. These workers also noted moderate colloid distention of the thyroid and testicular (interstitial cellular) hyperplasia in their autopsied animals. Hartman and his associates (120) noted too in cats a fairly constant hyperemic condition of the abdominal organs, and an accumulation of considerable quantities of lipoid substances in the convoluted tubules of the kidney. A definite increase in the kidney lipoid in adrenalectomized guinea pigs and rats has also been reported by Gunn, Cori and Hartman (111).

While severe disturbances of the gastro-intestinal tract and of other abdominal organs is evident therefore following adrenal removal, it should be emphasized that these conditions occur with the development of the acute symptoms of adrenal insufficiency. That similar conditions are present in many toxic and infectious diseases is also readily apparent. With the possible exception of the hepatic and pancreatic conditions, involving disabilities in the metabolism of carbohydrates, it is doubtful whether the foregoing changes would be considered of specific importance in adrenalectomized animals.

Prolongation of life after adrenalectomy: Oestrus, pregnancy, seasonal changes. Under certain conditions the life-span of animals after removal of the adrenals is notably increased beyond the usual limit of one

or two weeks. It is clear that accessory tissues may serve toward this end in many animals, particularly in rats and rabbits. In guinea pigs, cats and dogs this factor is rarely concerned, and only a few extended survivals are therefore observed. It is also difficult to prolong significantly the life of dogs and cats by cortical transplants, although with guinea pigs some success has been achieved (145).

Dogs which are pregnant or in heat when operated on outlast considerably the normal limits of life; seasonal influences on the survival period have been noted, too, in certain animal species. The administration of large amounts of fluid has also given symptomatic relief and prolonged life in many instances. Within the past few months the demonstration that an extract of the adrenal tissues can maintain adrenalectomized cats in apparently perfect health for indefinite periods marks a particularly important advance in this field.

A striking prolongation of life following adrenalectomy has been observed in dogs in "heat" by Rogoff and Stewart (234). In four animals they noted survivals of $21\frac{1}{2}$, 32, $36\frac{2}{3}$ and $64\frac{2}{3}$ days—periods far surpassing those found under ordinary conditions. Obtained on only a a small series of cases, these results appear quite definite, although they yet lack confirmation by other workers.

In pregnant dogs also similar remarkably long survivals were witnessed. The average noted by Rogoff and Stewart (230) in 17 cases was slightly over 22 days, and four of the animals lived 32, 46, $57\frac{1}{2}$ and 58 days respectively. Furthermore, one dog lived into the 26th day after the delivery of six pups, born just after completion of the adrenal operation. In the pregnant cat, very peculiarly, Corey (59) and also Rogoff and Stewart have found no such significant prolongation of life.

Several years ago it was reported by MacCallum (263), from investigations which had been carried out by H. A. Stewart, that pregnant or lactating cats survived adrenalectomy much longer than non-pregnant animals. In the former group an average life of a little over 7 days only was observed, however, and the longest survival was 11 days; moreover, the control animals lived only a little over 2 days on the average. Various possibilities were brought forward to explain the results: *a*, that changes in the ovary, particularly the presence of the corpora lutea, might compensate for loss of the adrenals; *b*, that mammary gland enlargement and function might be the effective factor; *c*, that the results were referable to chemical changes incident to pregnancy.

Rogoff and Stewart have recently reëmphasized the possibility that cells in the ovary and particularly the cells of the corpora lutea, which

are known to resemble those of the adrenal cortex, may be important factors in the long survivals of pregnancy. Changes connected with the oestral and pro-oestral periods, it is remarked, may exert an influence for a time in neutralizing the effects of adrenal insufficiency. Apparent relationships between the ovaries and the adrenals have long been considered and are treated at length in Vincent's monograph (291). The possibility of the corpus luteum of pregnancy acting as a "temporary cortical adrenal body" (Mulon) has also been discussed.

It is questioned by Rogoff and Stewart whether in the male a similar influence on the survival period of decapsulated animals can be obtained by procedures which are calculated to cause hyperplasia of the interstitial cells of the testis. Although it is perhaps possible that the fetal adrenals may act vicariously during pregnancy under the emergency condition which is imposed by adrenalectomy, the influence which is operative in the pre-gestational and post-partum phases is nevertheless still left unexplained.

The normal and considerable variations in carbohydrate metabolism which have been found in pregnancy may be noted in connection with the above very interesting disclosures. In pregnant animals, for example, there are observed much greater amounts of liver glycogen than in non-pregnant animals (Charrin and Gouillemonat). In the human fetus also it is known that relatively large quantities of carbohydrate are stored in the liver (Clogne). These points are probably of importance in view of the fact that serious derangements in carbohydrate metabolism are observed in adrenalectomized animals.

The marked increase in weight of the liver in pregnancy,—on an average 27.5 per cent in the rat (Herring), which undoubtedly represents a response of considerable physiological significance,—is also pertinent, possibly in connection with protein as well as carbohydrate metabolism. The economy which the pregnant organism exhibits in utilizing valuable protein materials has been discussed by Harding (114).

The oxygen consumption of individuals is sometimes lower during the menstrual period, according to recent observations (21)—a condition which again may have some bearing on the foregoing protracted survivals after adrenal removal.

The possibility also comes to mind that with the increase of lipoids which occurs in the tissues generally during pregnancy, provision may thereby be made for augmenting the supply of critical material normally furnished by the adrenal cortex, which is notoriously rich in lipoids.

It is interesting to note that seasonal variation in survival has recently

been observed in this laboratory (33) in mammals with the adrenal glands extirpated. Whereas the marmot (*Arctomys monax*) appears to succumb rapidly when the operation is carried out in the summer, very long post-operative survivals are observed in winter. A few animals perished when exposed during zero weather, while normal animals were unaffected. Significantly, too, the animals operated on and surviving through the winter have succumbed with the approach of warm spring weather—nearly all have died in April—when the marmot usually becomes active once more.

Such notable variations in response are possibly referable to the metabolism of this particular animal. In the summer it is vigorously active, while during the colder months it becomes torpid, although hibernation does not usually occur in captivity; little or no food is taken, the body temperature and blood sugar are considerably lowered, and the respiratory quotient reaches very low levels. That an autumnal diminution in adrenal activity might serve to bring about hibernation in such animals as the marmot has been suggested elsewhere (31).

These experiments are of peculiar interest in view of the older work of Abelous and Langlois (2) on summer and winter frogs. Whereas the former animals always died within two days after cauterization of the adrenals, the latter frequently lived for periods up to about two weeks. Increased (stimulated) muscular activity and also slightly elevated environmental temperatures induced early death. It was considered that the length of survival was in inverse ratio to the degree of chemical changes going on throughout the body.

Pertinent to the foregoing also are the observations on rabbits by Fujii (92). This worker found an increased adrenin content of the adrenal glands correlated with an increase in glycogen content of the liver in the early months of spring.

In thyroidless adrenalectomized animals, a slowing down of metabolism is suggested as the probable explanation of longer survivals than normal which have been observed by Zwemer (311). Courrier also, it may be mentioned, has noted seasonal variations in survival following castration in bats (68). Riddle (220) has drawn attention to marked seasonal changes which occur in size of certain endocrine organs and to the increase of liver weight during the reproductive period in pigeons. A report by Griffith et al. (110) indicates that in man also there occur important seasonal fluctuations in bodily activities.

From the large body of evidence which has been arrayed on adrenal physiology in the past twenty years or so particularly, it does not appear

that the glands can be considered to have a varying functional significance in different classes of animals, as was suggested by older writers. Accessory tissues indubitably answer for most of the widely differing survival periods observed. Death from adrenal insufficiency, too, is substantially similar in all animal types, as has been indicated.

While it would seem to be the normal expectancy that different animals, with constitution and diathesis and what not showing wide variation from individual to individual, would exhibit slightly different survival periods, interpretation of the greatly extended survival periods observed in the foregoing cases, excluding those with accessory tissues, is singularly baffling. Vicarious functioning of specific and related tissues in the decimated animal itself or in its offspring-to-be may be involved as having a slight bearing on the question, but the hypothesis is open to many criticisms and does not leave one with a happy feeling on the matter. For the present, dependency must apparently be placed on the broad generality of variations in "metabolism" by way of explanation, and theory be left to those with conjectural talent.

Influence of forcing fluids and other procedures. As early as 1898 Soddu (249) found that the symptoms of adrenal insufficiency in dogs were relieved slightly by saline injections. Banting and Gairns (14) considered that repeated saline injections prolonged the life of one of their 56 operated dogs. Normal and at other times 5 per cent saline up to 150 cc. was injected at frequent intervals. Concurrently the animal was also given large amounts—up to 195 cc.—of normal dog blood serum. Reduction of blood urea and non-protein nitrogen was observed following these procedures. While the dog lived 16 days after adrenalectomy, which is about twice the usual period and almost equal to Rogoff and Stewart's best-surviving untreated animal, it seems hardly possible to credit the experiment as indicative of the beneficial effects of saline administration alone. Hypertonic saline solutions such as Banting and Gairns frequently used have indeed been found by others (198) to be prejudicial to life in adrenal insufficiency.

Stewart and Rogoff (261a) have recently observed a remarkable prolongation of the life of adrenalectomized dogs injected with Ringer plus glucose solutions at frequent intervals. In 17 animals the range of survival was from 3 to nearly 54 days, and the average nearly 20 days; only 4 animals died in less than 10 days (table 1). This is nearly as good a survival record as that derived from untreated pregnant animals, and almost twice as good as Rogoff and Stewart's own animals which were given cortical extract.

Repeated injections of glucose which were given to dogs by Banting and Gairns prolonged life "a few hours" only, and kept the blood sugar up till the time of death. Numerous doses of adrenalin did not, according to them, extend the normal survival period. It has frequently been observed by the writer (34), it may be remarked, that small injections of adrenalin (0.02 mgm. per kilo intraperitoneally) will restore animals dying of adrenal insufficiency to an apparently normal condition. Animals (cats, dogs, and marmots) have been severely prostrated, sometimes in convulsions with marked hypoglycemia, and yet have shown recovery to lively activity coincident with an increase in blood sugar, after one or two injections of adrenalin hydrochloride. Glucose solution may be similarly effective. The tenure of life appears to be increased, however, only a few (5 to 10) hours at the most.

Several substances—physiological saline, Ringer's solution, and isotonic sodium acetate solution—were found by Marine and Baumann (198) to increase the life-span of cats suffering from adrenal ablation. Isotonic glucose and glycerol solutions appeared to have only slight effect. It was concluded from the experiments that diuresis was an important factor in determining the duration of life.

Glucose and normal salt solution, administered orally, were considered by Corey (59) more effective than a number of other substances in prolonging the life of operated cats. Zwemer (310) also found that 5 per cent glucose solution was efficacious when given by mouth.

Daily feeding of desiccated thyroid gland hastens the death of adrenalectomized animals, according to Zwemer, possibly because of the increased dehydration of body tissues which is brought about by this procedure.

Adrenal extracts. During the past ten years Rogoff and Stewart have tested numerous extracts of the adrenal cortex, obtained by many different methods, in attempts to substitute for the adrenals and prolong the life of adrenalectomized animals. Widespread discussion of their work has been aroused, and many sanguine hopes were inspired as the earlier optimistic results were reported orally and in the press. Although many important claims have been made for certain substances used by these workers, no methods of extraction have been mentioned, unfortunately. "Various salts" and "various solvents," it is divulged, have been used in making the preparations. In a short note it is mentioned also that fresh adrenals obtained from dogs were extracted with 0.9 per cent sodium chloride and glycerol. Extended protocols of experiments have been given in nearly all their papers.

The whole adrenal gland was used by Rogoff and Stewart for their extracts, and adrenalin appeared to be always present, as tested colorimetrically. It was nevertheless concluded that the results were not due in any *important* degree to adrenalin. The dose of the extract was stated to be 0.5 or 1.0 cc., usually given intravenously; it is difficult to catch the illumination from this disclosure, however, in the absence of data on the amounts of fresh gland used. There was no essential difference, they believed, between the results of intravenous injections of homologous and of heterologous material. The injection of an extract of sheep's adrenals was considered efficacious in prolonging the life of adrenalectomized dogs. No material which was kept more than a week or ten days was used. Rogoff and Stewart declare that they have now given proof that a substance can be extracted from the adrenal cortex which can prolong life after adrenalectomy.

Some of their animals, it is true, survived beyond the maximum period observed in the controls. One exceptionally long survival of 78 days was considered to be due to the administration of adrenal extracts. The next longest survival was, however, only 28 days. The period of good health was also considered to be extended, and pathological changes in the gastro-intestinal mucosa were said to be less common and less extensive in treated animals. Reference to table 1 will show the trend of Rogoff and Stewart's results in the past few years. The significance of such a trend has been referred to later.

The results of their treatment of adrenalectomized male and female dogs with adrenal extract are also given in table 1. They are stated by Rogoff and Stewart to be "strikingly positive" (233). Twenty-eight animals were treated (April 1928), and the average survival period was 11.9 days, with a range of 5.7 to 27.7 days. There were 13 deaths which occurred under 10 days. In the group, however, were 9 females, 3 of which lived 12, 16 and 27.7 days. All the females were nevertheless found non-pregnant, and also, as far as could be determined, not in heat. When present, these conditions tend, as Rogoff and Stewart have very definitely shown, to prolong considerably the lives of completely adrenalectomized dogs.

It should be mentioned that one particular case which was treated by adrenal extract has been omitted by the reviewer from table 1; it concerned an animal which survived over 78 days and which was obviously out of place in a group in which over 80 per cent of the animals survived less than 18 days, and almost 50 per cent less than 10 days. It appears that no extract was given throughout the last 40 days of the

animal's post-operative life, although it is asserted that the long survival could be attributed only to the injections (given during the earlier part of the experiment). Careful investigation did not disclose any accessory adrenal tissue, although no mention is made of microscopic search. The next longest-surviving animal in the same group lived slightly less than four weeks as against the eleven weeks' period of the foregoing extraordinary case.

It should be admitted that some of the animals which were treated by Rogoff and Stewart with adrenal extract lived beyond the normal expectancy of life following complete adrenal ablation. The results

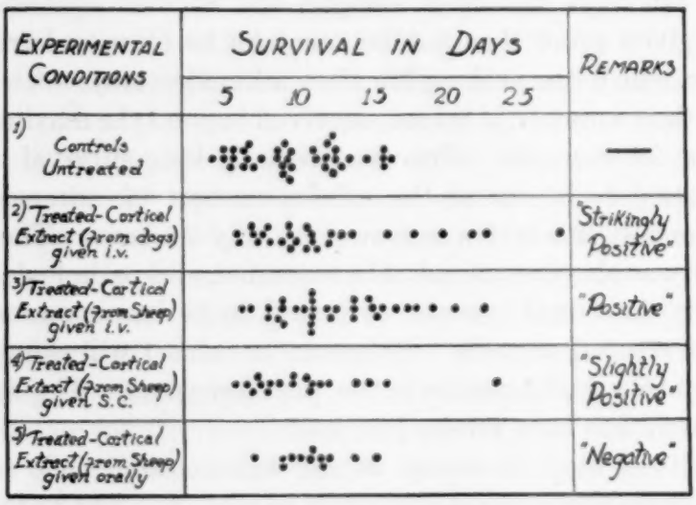

Fig. 1. Chart derived from data given in articles by Rogoff and Stewart, including their own remarks on the results, on survival of dogs after adrenalectomy. Record of one animal which lived 78 days after operation is omitted from group 2: it was given adrenal extract for only a small part of the survival period and no microscopic analysis for possible accessory cortical bodies was made. It is readily observable that most of the dogs (over 90 per cent) in all the experiments died within 17 days, which may be considered the outside limit for survival of control animals. That only very slight indication is given of any effect produced by extract administration is apparent.

are not, on the whole, very different from those derived from the control animals. From the rather gradual increase in the significant average figures of survival periods which are shown in Rogoff and Stewart's various experiments extending over several years—5.8 to 6.4 to 6.9 to 9.9 days for *control* dogs, to 11.9 to 12.5 days for *extract-treated* animals—one could readily draw an interesting and suggestive curve. In the interpretation of such a curve it would not seem *ultra vires* to ask whether

it represents a normal progressive increase in technical facility plus the slight effect of an unknown factor in the adrenal preparation—or only the operative factor. Reference to a chart of the results presented herewith (fig. 1) does not leave one with any positive feeling regarding the extract's efficacy.

A somewhat careful analysis of Rogoff and Stewart's results has been made because of the wide publicity they have obtained and the important claims which have been set down by these investigators. It is averred, for example, that the investigations have culminated in demonstrating for the first time that cortical extracts have been prepared which can supply something normally furnished by the cortical tissue, and can substitute for the adrenal gland; that the symptoms of adrenal insufficiency are ameliorated and that the pathological changes found at autopsy are less marked when the extract has been used. Clinical use of the material has been tried in a large number of cases of Addison's disease, and noteworthy relief of symptoms is said to have occurred. Considerable recognition of the work has been given in clinical publications (81a). The name "interrenalin" has furthermore been applied to the substance:

Extracts which have been made from sheep's adrenals and given intravenously have also been considered by Rogoff and Stewart to prolong slightly the life of adrenalectomized dogs (262a). Subcutaneous injection is said to have provided slightly positive results, while oral administration was negative (table 1).

Various extracts from ox adrenals were found to be ineffective by Banting and Gairns (14). An aqueous extract of dog's adrenal cortex was believed, however, to have prolonged the life of one dog from which the glands had been removed, although the animal lived only slightly beyond 7 days. This single experiment can therefore hardly be considered as positive, particularly in the light of the much longer-surviving untreated cases reported by Rogoff and Stewart.

The work of Hartman and his associates on cats would seem at first to offer a somewhat brighter ray of hope on a much-beclouded subject. They have used extracts of the adrenal cortex only; in over one hundred cases they have tested the potency of their extracts, and survival-periods for adrenalectomized animals about five times as long as the normal (for *their* technique) have been obtained; they have also reported various methods of extraction of the materials they used. Fresh beef adrenals which were chilled soon after removal from the animal were employed by Hartman. The cortex was carefully separated from the medulla, ground or finely chopped and shaken with three volumes

of water for 15 to 30 minutes. Solids were then separated by filtration or by centrifugalization. The clarified liquid served as the starting point for extraction of the cortical hormone by various procedures. Acetic and hydrochloric acid extracts were used in a considerable number of cases, and proved to be somewhat effective in increasing the survival period of adrenalectomized cats.

The results which were obtained with the use of sodium chloride preparations were exceedingly suggestive: over 50 animals lived from 2 to 80 days after complete removal of the adrenal glands, and about 50 per cent survived more than 20 days. One animal from which the thyroids and testes had been removed lived for 300 days after complete adrenal removal; two accessory cortical bodies were observed, however, at autopsy. In a number of the animals which were treated with cortical extracts, the metabolism remained within normal limits for two or three weeks after removing the adrenals, in striking contrast to untreated controls, although there was usually a loss of body weight. Animals which had begun to show asthenia were found to recover with cortical extracts, administered subcutaneously at first every 4 to 6 hours, and later twice daily. One animal which lived 80 days died, it was considered, because the extract was discontinued after 69 days.

Hartman and his associates found their best series of treated adrenalectomized animals (14 cases, treated with "Extract VIII") survived an average of 27.4 days. This compares with about 6 days for controls —a figure derived chiefly, it appears, from the work of other experimenters. It should be noted that 1 cc. of "Extract VIII" was equivalent, however, to 5 grams of cortical tissue, and that the subcutaneous injections which were administered per 24 hours represented material derived from about *40 grams* of adrenal cortex! And from many determinations it appears that only about 0.1 gram of cortical tissue per kilo of body weight is present in the whole cat!

It is well to note, furthermore, that an average survival period for cats of 11 days has been reported by Rogoff and Stewart. Hartman *et al.* have thus been rightly criticized because of their failure to publish satisfactory control experiments of their own. The name "Cortin" has been proposed for the material extracted by Hartman.

Efforts on the part of the Cleveland workers to reproduce Hartman's results do not appear to have been successful. Extracts which were prepared from the adrenals of cattle, in the manner described by Hartman and his co-workers, were found by Rogoff and Stewart to be ineffective when administered subcutaneously into dogs and cats (262a).

Given intravenously to dogs, the effects were shown to be slight—if indeed any definite effects were produced. They were not nearly so effective, it was claimed by Rogoff and Stewart, as their own extracts.

A great deal of credit must, it is true, be attributed to the latter workers for their technical facility, and the much longer survival-periods following adrenalectomy which they have achieved. In this connection it should be noted that their standard of judgment, i.e., the period of survival, is therefore considerably higher than that observed by Hartman and his collaborators. Furthermore, the short series of cases which have been treated by Rogoff and Stewart with extracts made according to the Hartman method can scarcely be accepted as negating wholly the potency of the material as tested in the hands of the original investigators. It is really to be regretted that others have to date been precluded from testing the allegedly potent extracts fabricated by Rogoff and Stewart.

Attempts by Swingle and Pfiffner (276a) to reproduce the results of Hartman have also met with failure. These workers consider that Hartman's extract is inactive or at best possesses only an extremely low potency.

An extract that maintains adrenalectomized animals in perfect health. Brief preliminary reports only have appeared of recent experiments by Swingle and Pfiffner (274, 275), although these workers have to date undoubtedly achieved most praiseworthy and remarkable results in their investigations on the adrenal cortex. In less than a page report, they have given their methods and chief results. Beef adrenal glands from which the potent materials were extracted by means of organic solvents were employed. The cortical tissue was ground and extracted at room temperature for 24 to 48 hours, with 95 per cent and later 85 per cent alcohol. The extractives were concentrated separately in vacuo at a low temperature, and the residues extracted with benzene. The lipoidal residue was freed from the last traces of benzene with absolute alcohol, and then dissolved in corn oil. It was administered subcutaneously, 1 cc. of the finished extract being equivalent to 30 grams of fresh cortical tissue. The extract retained its potency for at least three weeks when kept at 6°C., and active extracts were obtained from cortical tissue stored in 95 per cent alcohol at room temperature for as long as two weeks. Varying degrees of potency were observed—one, "no. 132", was particularly effective.

It was shown by Swingle and Pfiffner that the life-span of 20 of their control cats averaged 6.9 days, with a variation of 4 to 13 days—a con-

siderably lower average, it will be observed, than that shown by Rogoff and Stewart. In contrast, extraordinary increases in the life of adrenalectomized animals which were treated with cortical extract were observed. In 20 cases, the least period of survival was 17 days, and the greatest (up to the time of the first report) 50 days; only 2 of the treated animals survived less than 20 days, and 50 per cent lived beyond 30 days. The average survival period for the 20 animals was 31.9 days—a truly astonishing record in view of all previous results in this field.

A further short article by Swingle and Pfiffner which has just appeared (276) indicates that an aqueous extract of the adrenal cortex which they have now obtained is markedly potent in sustaining the lives of adrenalectomized cats. The method of extraction, which is again given in brief, is substantially similar to that quoted above. The alcohol is removed and an aqueous solution made up, clarified and sterilized for subcutaneous injection by filtration through a Seitz filter. The solid content of this extract varies between 5 and 10 mgm. per cubic centimeter. It is not, however, entirely free of adrenalin.

It is affirmed that operated animals treated with 0.5 to 1.0 cc. of the extract per kilogram of body weight daily, by subcutaneous injection, remain in perfect condition for very long periods. They gain weight and cannot be distinguished from normal unoperated cats. In several animals which were sacrificed on the fiftieth day of survival in order to ascertain whether accessory adrenals were present, no trace of such tissues was found after the most exhaustive search. The longest surviving animals were reported to be lasting up to the 80th day, and were still showing excellent condition. Use of the earlier lipid extract, it is mentioned, resulted in troublesome abscess formation and other difficulties, after frequent subcutaneous injections of the material.

A few points should perhaps be kept in mind in attempting to evaluate the foregoing results. 1. Extracts of the *whole* adrenal gland have been used. 2. Relatively huge amounts of the extract were given—1 cc. of the material was equivalent to 30 grams of the fresh cortical tissue, and from 0.5 to 1 cc. per kilo body weight was injected; thus, extract derived from 50 to 100 grams of cortex, or approximately 150 to 300 times the amount of cortex present in the whole cat, has been given daily. 3. The extract has to date been shown to be effective *only* when adrenalin is contained in it. 4. A small percentage only of the animals used are able to be kept alive for significant periods after adrenalectomy. 5. Satisfactory proof must be presented that long-surviving animals possess no accessory cortical tissues. And 6, it has not yet been fully

ascertained that *indefinitely* long survivals are possible with the use of the extract. Supplementary masses of adrenal cortex may apparently be present in cats, it should again be emphasized, in 8 or 10 per cent of cases.

In private communications Doctor Swingle states that a method has been perfected for removing all traces of adrenalin from the extract, which is now also rid of 99 per cent of solids. Later, however, adrenalin has been found in the extract by use of the intestinal strip method.

The exceedingly suggestive and important results which have been reported by Swingle and Pfiffner, in brief only but none the less emphatic, inspire the hope that the life-span of completely adrenalectomized animals may eventually be extended indefinitely by the use of cortical extracts. And this inescapable condition must obviously be met before the presence of the hormone in an extract in acceptably significant amount can be considered valid.

It appears reasonable to suppose that *traces* of the elusive cortical hormone are present in the materials recovered by Hartman and his associates, and also by Rogoff and Stewart. "Cortin" and "Interrenalin", their laboratory offspring, can hardly be credited further, however, according to the published reports and those which, if sundry public discourses are indicative, appear in the offing.

Delightfully in contrast, the present patient conservatism of Swingle and Pfiffner, with an agent in their hands apparently far superior to any yet devised, unnamed and unsung in the advertising arena of clinicdom, lends not only enchantment to, but more than a modicum of confidence in, the inherent possibilities of their work.

In further communications received since the above was written Professor Swingle states that he is able to keep all his adrenalectomized cats alive with the aqueous cortical extract which he has developed. Moreover, not a single animal has shown symptoms of adrenal insufficiency while undergoing treatment. If the extract is withdrawn, however, marked symptoms develop in a few days, although restoration to a normal condition can be brought about within 3 to 5 days by recommencing the injections. Death soon follows if the extract is not given. "Several" cats have been kept in perfectly normal condition, it is said, for 100 days. It appears that all the extracts used still contain adrenalin in small amounts.

In the latest preliminary note published by Swingle and Pfiffner to date (276) a table shows that one adrenalectomized animal survived from December 24 to April 3, and gained steadily in weight from 3185

to 3835 grams during that time. On the latter date the extract was discontinued, while the animal was still in perfect health; symptoms of adrenal insufficiency appeared on April 8, and the animal died on April 11, after a rapid fall in weight to 3355 grams had taken place. Again, it may be stated that the far-reaching importance of such results cannot be over-emphasized. It is furthermore observed by the Princeton investigators that, so far as is known, all animals receiving the adrenal extract would survive indefinitely, although the treatment is stopped at the end of 100 days. Male cats have chiefly been used. The fractions of the extract which contain the cortical hormone can now be stored in benzene or alcoholic solution. More complete details of these outstanding and apparently conclusive investigations are now keenly awaited.[2]

Effects of extracts used by various workers. Many other experimenters have at different times reported on the beneficial effects derived from particular extracts of the adrenal cortex. Marine and Baumann, who amongst others have worked on the problem for several years, apparently kept adrenalectomized cats alive a few days beyond the limits observed in their control animals with the use of hydrochloric acid extracts.

Evidence which has been put forward by Goldzieher (103) calls for passing mention. It is claimed that a potent extract of the cortex, designated "interrenin," has been isolated from beef adrenals, by a detailed chemical process; it is asserted that its efficacy has been demonstrated on adrenalectomized rats! Outstanding (depressant) effects of the material appear to be produced on the respiratory rate (as observed in the clinic) and the blood pressure level (104). Many considerations point to the immaturity of this work, although priority for discovery of the cortical hormone has been claimed (102).

Assertion has been made by Koehler (154) that adrenalectomized dogs can be kept "alive and well" with an adrenal extract which he

[2] At the time of going to press the Swingle-Pfiffner extract is being tested with some indications of its efficacy on Addisonian cases in important hospitals (Johns Hopkins and the Mayo Clinic) in the country. Further evidence of the striking effect of the substance on animals has also been reported (Science, 1930, lxxii, p. 75). In this Laboratory a preparation of the extract made according to the method published by Swingle and Pfiffner was effective in prolonging the life of one animal (cat), after severe symptoms of adrenal insufficiency had become apparent, for four days—when our limited supply of material was exhausted. Hartman and his coworkers still vigorously maintain that their extract possesses marked potency (Science, lxxii, p. 76), in the face of adverse findings in other laboratories.

developed two years ago. In brief reports since then it has been stated that the extracts, now considered adrenalin-free, are able to raise the metabolism of dogs and mice (157), but the critical test of maintaining life after adrenal removal has not been satisfied.

The hypercalcemia which occurs in animals following adrenal ablation may be diminished by the administration of extracts of the cortico-adrenal tissues, according to Taylor and Caven (283).

Experiments which have been carried out by Kisch (152) on selachians indicate that the fatal results of interrenalectomy in these fishes may be delayed by administering acid extracts of interrenal tissue. The difficulties met with in attempting to excise the interrenal tissues, however, necessarily led to widely varying results in this work.

Various effects of cortico-adrenal tissues (desiccated) on the growth of chicks have been noted by Eaton and his associates (81). In rats an extraordinary formation and deposition of fat was attained with the use of various cortical preparations by Hewer (126). Effects produced by cortical extract have been observed by Marine, Baumann and Cipra (199) on heat production, and by Huth (139) on the regeneration of blood cells.

Muscle contraction curves derived from the gastrocnemius muscle of adrenalectomized animals (guinea pigs) were observed by Kühl (160) to be markedly increased after fatigue had set in by adrenal extracts said to be free of adrenalin. Cardiovascular effects produced by cortical extracts have also been reported by Gherardini (99). The muscle-fatigue method of evaluating cortical extracts as used by Kühl has been criticized by Florey *et al.* (90). It has been stated by Sun (269) that amino-acid production in the muscle-tissue of guinea pigs is accelerated by fresh cortical (as well as medullary) adrenal tissues. It is not at all indicated, however, that any of the materials used in these experiments represent true effects of the cortical hormone.

Amongst many others, effects of adrenal extracts on muscular contraction have also been noted by Obré (210), and Stefl (252).

A substance with marked reducing properties, designated "C_{XII}" has been obtained by Szent-Györgyi (279) by extracting the cortex of frozen adrenals with methyl alcohol. The material does not appear to alleviate the symptoms of adrenal insufficiency. The substance is considered specific for the interrenal system, and has recently been isolated in a crystalline form. It is stated to be a hitherto unknown isomer of glycuronic acid. It inhibits pigment formation and is said to be active in very minute quantities. Fuller details than are given in the preliminary report of this work are awaited with interest.

Attention has been called to the extraordinary lability of adrenal cortical extracts by Putschkow and Krassnow (216).

Further considerations on the chemistry of the adrenal cortex have been brought forward by Woodhouse (301) and Stefl (252). Observations on the high content of glutathione (Blanchetière and Binet; Binet and Giroud) and of sulphur (Loeper *et al.*; Lurie; Aufrecht and Diesing) in the adrenal tissues have also been recently published.

Cortical and medullary considerations. The intimate anatomical relationship of the adrenal cortex and the medulla in higher forms naturally led many years ago to belief in a physiological affinity of these tissues. The phylogenetic history, suggestive of correlated function, that is presented by adrenal development—from the separate systems in fishes, to the gradually higher type of intermingled interrenal and chromaffin tissues in amphibians, reptiles and birds, to the well-defined entity in mammals—is undoubtedly important and highly interesting. Nevertheless, there are other considerations which come into the picture. The distinct embryological and histological differences between the two tissues are fairly well understood and should be noted; also, the markedly different staining reactions of the chromaffin medullary and the lipoid-bearing cortical tissues are readily appreciated. In the presence of such widely different morphological characteristics, it is therefore hardly to be expected that functional homogeneity would be found.

That adrenin may be secreted by or preformed in the adrenal cortex has been contended by numerous authors for many years. Some investigators have recently reported (69, 119) that the presence of adrenalin may be detected by various methods in the cortex of the gland. That this may be accounted for by a very rapid diffusion process, which apparently takes place after death of the animal, should however be borne in mind. Banting and Gairns have drawn attention to this possibility. They have found that when the cortex is shaved off *in vivo*, or within 2 minutes after arrest of the blood flow through the gland, no adrenalin can be detected in the tissue by the colorimetric or biological tests. *Two hours* after the death of the animal, however, adrenalin could be demonstrated even in the outer layers of the cortex. Extracts of the interrenal bodies of elasmobranch fishes which have been made by Lutz and Wyman (187) also do not give the usual tests for adrenalin.

In a previous section the apparent involvement of both cortex and medulla in influencing various phases of carbohydrate metabolism has been discussed. It may however be stated that while the possibility of a functional relationship should be allowed for the present, the evidence

on adrenal function which has accumulated over many years, although in many respects unsatisfactorily indefinite, has not given support to the idea.

It has been amply shown that the adrenal cortex or its secretion is essential to life. Indeed it apparently represents one of the most important tissues, when considered quantitatively, in the whole body; deprived of it, the organism invariably perishes within an extremely short period. Although on ordinary inspection an animal may appear in fair health for a few days following adrenalectomy, there are many considerations, to be recounted later, which indicate that demoralization of the normal bodily processes begins very soon after the operation. Numerous observers have confirmed the opinion held for some years past that it is the cortical tissue *sui generis* which is of outstanding importance in maintaining life (Wheeler and Vincent; Elman and Rothman; Wislocki and Crowe; Zwemer; Houssay and Lewis).

These workers, extending the earlier findings of Biedl and others, have shown particularly that animals may continue to survive when only a small remnant of the adrenal cortex is left *in situ*, but that removal of the remnant quickly results in death. In his review, Hoskins concluded that the cortex was probably the indispensable part of the adrenal. Apparently about 10 per cent of the principal cortical tissue in the body, or an equivalent amount of accessory tissue, may sustain animals for at least considerable periods in tolerably good health. Certain deficiencies may be readily demonstrated in the animals that survive, and in many instances it appears that only a threshold existence is maintained.

Many animals succumb with all the symptoms of adrenal insufficiency, even when notable amounts of microscopically normal adrenal or accessory cortical tissues are present. Stewart (254) has found that the mortality from sub-total operations is very high. It is well known too that a fatal outcome in Addison's disease frequently occurs while recognizable masses of cortical and medullary tissues still persist. Unquestionably there must be a minimal (critical) amount of functioning cortex in the body, possibly proportional to the weight or surface of the animal, with which life may be sustained under quiet conditions, although in constant jeopardy; possessing less than such a critical amount, or lacking the necessary secretion (which may now apparently be supplied as an extract), life is impossible.

While the pendulum has thus swung very definitely toward attributing to cortico-adrenal activity the major rôle in the maintenance of life, it has nevertheless not seemed, at least until recently, that the available evidence ruled out entirely the possibility that the medullary tissues were vitally essential. The widely-distributed chromaphil elements should of course be included with the medulliadrenal mechanism, even as the accessory cortical bodies are to be grouped with the principal cortical tissues in the main adrenal glands.

In a recently-published monograph (104) it has even been stated that "it is a matter of contention whether the medulla or the cortex is the more important part of the organ." It has also been remarked by Abel (1) that the cortical portion of the adrenal gland contains a hormone which is more *immediately* necessary to life than that produced in the medulla, and possibly this is a true representation of the case. Abel has furthermore protested against the conclusion formed by some experimenters that the chromaphil tissues are not necessary for life, in view of the fact that almost insurmountable operative difficulties, in the removal of all the widely diffused chromaphil tissue, practically preclude exprimental proof. More recent evidence appears, nevertheless, to have met successfully the difficulties involved.

Experiments which have been brought forward by Cannon and his associates (46) offer strong support for the argument that all the chromaphil tissues—those in the (peripheral) sympathetic system included with the adrenal medulla—may be dispensed with, without very serious interference to life. In one animal in Cannon's series which lived almost twelve months after operation in apparently good health, there was no indication by the denervated heart method of functioning chromaphil tissue. After sacrificing the animal for purposes of examination, the chromate test, applied to the abdominal vessels between the kidneys to ascertain the presence of accessory chromaphil filaments, proved negative. The previously demedullated adrenal (one gland had been extirpated) also gave a negative response to the test.

It should perhaps be recalled that the chromaphil bodies are found (291) in any part of the body into which the sympathetic system extends. More particularly they are present, it is well known, as very small groups of cells in connection with the abdominal sympathetic and its extensions. The frank admission by Cannon that according to his own experiments "the chromaphil tissue is not of *vital* importance," should have a distinctly salutary influence on the rabidity of those who have heretofore unwarrantably imputed to the Harvard investigators various assertions regarding the interpretation of adrenal function.

It has been shown by Campos et al. (39), it may be observed, that under certain conditions the suppression of medulliadrenal secretion does not appear to affect significantly the ability of a dog to perform routine work. Again it has been noted (35a) that cardio-acceleratory abilities under emotional stress do not appear to be notably disturbed after elimination of the adrenal medulla, but *with the cardiac nerves intact.* And it now appears that Cannon has established the dispensability, without at least serious danger to life, of all the medulliadrenal and extra-capsular chromaphil tissues.

It is wholly to be expected that these findings will stir up within the breasts of some few investigators who have hitherto strenuously opposed the Cannon school vigorous contentions purporting to show the impotency of the much-debated chromaphil elements in the body. It should scarcely demand the note here that dispensability, however, does not signify inutility—that organs which may be ablated without obvious immediate peril should not straightway be dubbed functionless. A medulliadrenalectomized organism has been shown frequently to be a defective organism, and medulliadrenal insufficiency is no less certain although a less manifest and less serious condition than cortico-adrenal insufficiency.

The very protracted series of negative experimental reports on medulliadrenal function which were published throughout many years by Stewart and Rogoff, and which eventually and unfortunately approached a style even diatribic in character, appear now to have given way to sundry verbal parries and thrusts unsupported by experiment and therefore with but little persuasive force (225, 256). In a review by Stewart it is said to be "impossible to assign to the medulla any function of physiological importance," although he is "loathe to conclude that it is the *roi fainéant* of the endocrine glands" (256). The wonder is indeed that under the circumstances a regal appellation of even a baser sort should be chosen simply to castigate this lowly pariah among splanchnic organs!

Rogoff also has recently contented himself in a review article with reiterated asseverations on the functional impotency of the medulliadrenal tissues, and has apparently been totally unaware of the large volume of forceful evidence which has come from laboratories other than his own within the past ten years or more (6, 17, 122, 135, 153, 285). In a brief rejoinder entitled "Endocrinology by Ukase" this peculiar and unfortunate attitude on the part of a scientific worker has been most aptly, albeit negatively, evaluated (43).

It is quite interesting to recall here that Addison's contentions regarding the importance of the adrenal glands met with very strong opposition in his day. Belittling remarks were passed by the learned Chairman in charge of the meeting at which Addison presented his classical report, and "Mr. Cock" was also very derogatory and "did not think they (the adrenals) performed a very important office." "Mr. Waterworth" fully concurred and proceeded to prove (!) that the glands were of little consequence in the body (3).

From the majority of countries in which physiological science is given accredited standing there have issued within the past decade results which are significantly concordant with those of Cannon and his associates, and contradictory to those presented by Stewart and Rogoff (6, 122, 153). Using the same methods which were employed by the Cleveland workers, quite opposite results to those of Stewart and Rogoff have in fact been recently obtained (268).

Particularly within the past few years the service that adrenin secretion renders in the stress as well as the routine of life has been abundantly proved by workers of the Harvard school. In the chemical control of body temperature, in various phases of carbohydrate metabolism, and in emotional as well as in severe muscular reactions the adrenal medulla exercises a specially important fortifying influence (41, 42, 44, 45).

A recent series of experiments by Wyman and his associates has emphasized too the functional significance of the adrenal medulla as distinct from that of the cortex. Specifically, in resistance to toxic factors and conditions producing shock it is shown that adrenin secretion plays a major rôle. Wyman has suggested (306) that the cortex is concerned in "the steady maintenance of proper vascular tone and blood volume through the depression of the production or liberation of vasodilator substances, while the medulla is ready to produce rapid adjustments in such emergencies as anaphylactic shock or acute intoxication."

Dale (74) has recently pointed out the admirable abilities which adrenin possesses for reinforcement of various bodily mechanisms. The very considerable number of papers which have accumulated within a decade or so have, however, been well reviewed within the past year (41, 42, 44–46), and this phase of the subject does not appear to call for further comment here. Derived from an overwhelming body of evidence it can be justifiably concluded that the medulliadrenal mechanism along with the sympathetic system, dispensable in the protected conditions of ordinary laboratory life, typifies its great service to the

organism at times of critical emergency, when it serves to adjust the pertinent visceral and somatic systems in the body to ensure the optimum response to external exigencies.

Adrenal insufficiency and Addison's disease. The first announcement by Addison in 1849 that a very peculiar type of anemia associated with severe muscular weakness was related to a marked pathological condition of the adrenal glands did not at the time evoke considerable comment. The London Medical Society passed over the presentation with but little discussion, part of which was indeed quite derogatory (3). The short but beautifully illustrated monograph which was published a few years afterwards (4) also passed off at first as a curiosity. Apart from the epochal scientific advance which it measured, however, the dignity and profound humility of his book, *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*, in an age of "bias and prejudice. . . . inseparable from the hope and vanity of an original discovery", are worth noting and indeed charming.

Addison's achievement is said by his contemporaries to have resulted from an exhaustive analysis of every organ of the body (299), and his own reference to "stumbling" upon the discovery should probably be attributed to innate modesty rather than actual fact. His senior Bright had amongst others previously described (1829) a case of adrenal insufficiency (case V. in Addison's memoir), without appreciating the related significance of the disease picture and adrenal involvement (124). Henry mentions other cases similarly unfruitful in reaching the truth which were published previous to 1855. The volume on "Medicine" which was written by the famous Bright and Addison (30)—chiefly it appears by the latter (299)—does not relate the glands to any disease condition, although Bright had had opportunity (as mentioned above) to do so.

While acclaim of Addison has thus been well-placed, it may be observed that several of his eleven collected cases are of doubtful classification: four showed an extensive carcinomatous condition which probably caused death, and three others were complicated by extra-adrenal disease. Some of these cases, it is clear, would not be arranged today under the disease known by his name.

In view of the many reports of favorable results which have recently been said to follow various forms of treatment of Addisonian patients, it should also be remembered that in several instances of the disease—two of which were "well-marked"—Addison himself noted that recovery took place under treatment. One case, he very interestingly remarks,

"appeared so hopeless in the hospital that he was left to Nature; but he got well under large quantities of brandy ordered by the clinical clerk" (3). This appears by the way to be the first case on record of the cure of apparently hopeless adrenal insufficiency—and that by a quite obscure experimenter, a clinical clerk—by an alcoholic preparation!

Amongst other symptoms, anemia, languor, debility, irritability of the stomach with impairment of the appetite and occasional vomiting, feebleness of heart action, and a peculiar change in color of the skin—such that a white person might be taken for a mulatto—were emphasized by Addison as features of the disease. Besides the invariable adrenal involvement, it is also noteworthy that gastric ulceration and renal lesions are also mentioned in the postmortem notes. It is to be observed that many of these changes are also present in experimental adrenal insufficiency, as has been pointed out in the comparisons made above. Very little—with the exception of certain changes in the blood—appears to have been added to the original description of the disease, although numerous theories have been advanced to account for the condition.

The possibility that any morbid affection of the whole adrenal gland might produce the symptom-complex was at first held by Addison. Some time later, a disturbance of the sympathetic nerves was considered by Addison and others as responsible in part at least for the disease. For a considerable period the lesions were regarded by numerous writers as particularly referable to the adrenal medulla. This view appears indeed to be held by many authors even today.

In a monograph which was published not many months ago (159) the assertion was made that "the symptom-complex associated with adrenal insufficiency (i.e., Addison's disease) rests on a subnormal output of adrenalin." Goldzieher in 1929 (104) introduced some considerations which he believed provided direct evidence that "phaeochrome insufficiency" and also sympathetic affections were very important factors in the etiology of Addison's disease. Not many years ago Langdon Brown (36) concluded that Addison's disease was essentially due to absence of adrenalin from the circulation. It has also been very recently stated that "opinion is by no means unified today as to the relative importance of cortical and medullary portions in determining the disease picture" (172).

The work of Wiesel in 1903 (298) appears to have shaped the trend of general opinion in this direction for many years. The extraction of

adrenalin and the avalanche of experiments on medulliadrenal function during the past twenty years served furthermore to put greater emphasis on the medullary portion of the gland as the apparently preëminent functioning tissue. While this general conception has now been proved invalid, it held sway for many years and gave many clinicians—and others—fairly fixed ideas on the subject.

In a recent contribution by Brenner (29) the conclusion is drawn that the symptoms of Addison's disease occur only when most of the cortex is destroyed. The symptoms may be present, it is shown, even if the adrenal medulla and the chromaffin tissues are normal, or again they are sometimes absent in cases in which there is almost complete disappearance of the chromaffin system. Five cases are reported, in four of which there were notable cortical lesions and little or no disturbance of the medulla; in the other, no evidence of the adrenal glands could be found. The literature is reviewed critically and at length, and it is shown that in forty-one quoted cases of Addison's disease the foregoing contentions are rather well borne out. It should nevertheless be remarked that in a few cases some cortical cells were present, although the medullary tissues had been obliterated. It is well to remember also in this connection that under experimental conditions life is often not sustained even though 10 to 20 per cent of normally appearing cortical tissue be present.

The observations of Brenner appear to be very suggestive. Studies by others (239) have led to the conclusion that Addison's disease and other less severe forms of adrenal insufficiency are the result of interference with cortical rather than medullary function. It may be recalled too that in some cases (23) Addison's disease has been described even when the adrenal glands have apparently been intact. The possibility of hypofunction of the cortex, as well as the recognized difficulty in definitely diagnosing the condition, must however be emphasized in this connection.

In contrast to Brenner's observations above are also the results reported recently by Barker (16a). In 28 cases of Addison's disease which were autopsied, 25 showed tuberculous lesions, and it was noted that in these there were appreciable amounts of cortical tissue present, occurring as small islands up to about 10 per cent of the normal amount in man, in all cases but one. This was the only exception, too, in which the patient had shown no pigmentation. Diffuse degenerative changes in the renal tubules were found in a number of the cases. A good review of the subject also is given by Barker (16a).

It has been suggested (29) that the Addisonian symptom-complex is referable to a necrosis of cortical cells caused by some unknown toxin with a special affinity for these tissues. Focal regeneration with the production of islands of hypertrophied cells is then considered to take place. Again, the possible emotional pathogenesis of the condition has been referred to by Marañon (195). Frequent involvement of the thyroid gland in Addison's disease, and relationships to hyperthyroidism, have recently been discussed (29, 141).

The superposition of Addison's disease on the diabetic condition has been marked, it is interesting to note, by extreme sensitivity to insulin administration (287). A definite refractoriness towards insulin was found to develop, however, in a case of diabetes which was complicated by cortico-adrenal hypertrophy (205). In his monograph, Kuntz (205) draws attention to the severely diabetic condition which chromaffin tumors involving the adrenal glands may evoke. These observations are indicative again—other comment would be premature—of the widely ramifying interrelationships of these organs of internal secretion.

Jaffe (144, 145) has presented experimental evidence of the interactivities of the gonads and thymus with the adrenal cortex, and has emphasized particularly the occurrence of thymic hyperplasia under different conditions following adrenal removal. Further connection of the little understood condition of status thymicolymphaticus with adrenal dyscrasias, often commented on clinically, is thus apparent.

Patients with Addison's disease have hardly ever been afforded noteworthy relief by the various means which have been tentatively employed towards this end, and the condition almost invariably leads to death within a year or two. The effect of adrenal transplants has in some instances been considered alleviatory (175, 217). Pybus has recorded striking results from grafting adrenal tissue taken from another individual into the supraclavicular fossae of the patient: the symptoms and even the pigmentation disappeared and the man was able to resume his normal duties. A second operation was carried out when the symptoms returned at the end of 2½ years, and again marked improvement was observed. At the time of the report the patient had been kept in fairly good condition for about 8 years in all, it appears. The exceptional survivals which have been observed in adrenalectomized experimental animals, kept in apparently perfect health with small cortical transplants, lend hopeful emphasis to the foregoing, although the different circumstances are of course readily recognized.

Many Addisonian patients were said by Rowntree (240) to be bene-

fitted on feeding desiccated whole adrenal gland by mouth. Koehler and his associates (156, 157) have also stated that elevation of the basal metabolic rate and marked general improvement in various types of clinical asthenias followed the administration of an adrenalin-free extract of the adrenal gland. Lacking more specific data on the observations of the latter workers, however, no evaluation of the abstractly-reported results can be made.

A cortical extract which has been prepared by Koehler (154) has been alleged to possess remarkable abilities: in cases of adrenal insufficiency; it removes the asthenia and fatiguability and enables the patients to gain weight, restores the respiratory disturbance, elevates the metabolic rate. . . . and gradually the blood pressure becomes elevated!" Two cases only are quoted, although a large number of cortical (adrenal) deficient patients are said to have been treated. Adrenalectomized dogs are said also to be maintained in good health with the extract. It is passing strange that for two years since this report nothing further of particular importance regarding the clinical use of Koehler's extract has been forthcoming.

In seven cases of Addison's disease which were treated by Rogoff and Stewart (239), "improvement" is said to have followed the administration by mouth of an extract prepared by them from the adrenal glands. Systolic arterial pressure and body weight were said to have been considerably increased, and fatigue was diminished in several cases. A few patients also showed lessened discoloration of the skin. These are very important results, if indeed they can be attributed to the potency of the material used. Improvement was apparently not noted, however, until a few weeks to about two months after treatment had been started. Moreover, some of the patients had previously shown spontaneous remissions—in keeping with the oft-observed progress of the disease. It also appears doubtful that all were true cases of Addison's disease. In a footnote, Rogoff and Stewart state that they observed improvement in two new cases within about two weeks after commencing treatment with the extract. It is again to be regretted that at the time of this writing no further development of this work is at hand.[3]

It is not within the province of the present paper to dilate at further length on the somewhat hazardous clinical aspects of adrenal insuffi-

[3] Sundry reports at scientific meetings and in the press, and personal communications, indicate that the cortical extract developed by Swingle and Pfiffner may be of distinct value in the treatment of Addison's disease.

ciency. Perhaps in no other phase of the subject is it more trite to urge that rigid precautions be taken before making deductions from a few experiments. The deplorable cluttering of the literature has not yet abated, and the *post hoc ergo propter hoc* kind of reasoning still runs widely rampant.

While there has been a definitely growing tendency to attribute Addison's disease to a cortico-adrenal affection particularly, and experimental results on adrenal insufficiency tend to be confirmatory, the evidence at present does not favor undeniably this viewpoint. The great mass of clinical material that has accrued in almost 80 years since Addison's paper appeared does not seem indeed to allow exclusion of medulliadrenal involvement. With the knowledge in mind of the diffuse tuberculous condition which is so often present in the disease, one can hardly see any way of escape from injury of the readily reacting medullary tissues.

Attention may be directed to the recent reviews of a considerable number of cases of adrenal (particularly Addison's) disease by Brenner (29), Barker (16a) and others (247, 195, 240).

It has been commonly considered heretofore that the clinical complex of Addison's disease cannot be reproduced experimentally in animals. For a number of years this seems to have held true, although it now appears that many of the changes recognized originally by Addison in several of his cases are to be found in the longer-surviving animals in the laboratory. The recent intensive application of physiologists to adrenal studies has in fact indicated several points of similarity of experimental insufficiency to the disease process in man. For example, the marked asthenia, with rapid fatigue on slight exertion; the low resistance to infection; the gastro-intestinal conditions, nausea, vomiting and occasional diarrhea; the low arterial pressure, subnormal body temperature, and hypoglycemia; the increase above normal of the nitrogenous constituents of the blood; the terminal convulsions and coma, and sometimes sudden death—these are all conditions which have been observed in adrenal insufficiency and Addison's disease alike. Bearing in mind the exceedingly rapid disorganization of the organism following adrenalectomy as contrasted with the long-drawn-out disease in man, it appears peculiarly significant, indeed, that the two processes present such characteristic points of resemblance.

Absence of chromatosis—very variable even in Addison's disease—under experimental conditions is possibly referable to the brief survival period after adrenal operation, as well as to the radically different in-

tegumental coverings possessed by the animals used. Pigment depositions have been said to follow shaving of the skin, however, in certain cases described by Kellaway and Cowell (151), and they have also been reported by a few of the older observers.

It is indicated in recent "ultimate" chemical analyses by Spohr and Moore (251), who have given a good review of the literature, that the pigment which is found in Addison's disease is definitely a melanin. The tuberculous toxemia which is usually present and which leads to a very gradual ablation of the adrenal tissues, with very wide scope therefore for hypertrophic and regenerative changes to influence the picture, should also be borne in mind in making the foregoing comparisons.

That many of the phenomena of Addison's disease are similar to those observed in animals suffering from adrenal insufficiency was suggested long ago (23) and has been more recently maintained by Snell and Rowntree (247). It has also been remarked by Rogoff and Stewart (239) that certain symptoms in both conditions, though varying in severity, are *qualitatively* the same and are to be considered as a part of the manifestations of adrenal insufficiency. One symptom commonly observed in long-surviving adrenalectomized dogs and very frequently reported by patients with Addison's disease, the latter observers note, is an aversion to foods which are rich in fats. Rogoff (225) points out that several symptoms—the anorexia, gastro-intestinal disturbances, muscular asthenia and nervous manifestations—are often found in both the clinical and experimental conditions.

Partial adrenalectomies on man. Operations entailing unilateral removal of the adrenal gland have been carried out within the past few years both in this country and (chiefly and perhaps happily) abroad. Apparently the serious technical difficulties involved have hitherto provided a deterrent sufficient to keep the number of operations on man relatively low.

Assuming that the activity of the thyroid is under the control of the neuro-adrenal mechanism, Crile (71) has proceeded to perform 10 "adrenalectomies" (obviously unilateral) in order to relieve the hyperthyroidism. No specific data of the results achieved are reported.

Leriche and Stricker had up to about two years ago (174) carried out 13 unilateral adrenalectomies for different vascular diseases, and noted slight improvement in the condition of the patients. One of the individuals who submitted to the operation was indeed of the Hippocratic profession! In attempts to alleviate endarteritis obliterans and Buerger's disease (267), and gangrene due to arterial spasm (67), other

practitioners have also adopted surgical removal of one of the adrenal glands.

The remarkable total of 130 left-sided adrenalectomies in man had been reached by Oppel up to a year ago when the good work was evidently still "going strong" (212). The operations were performed chiefly for the alleviation of spontaneous gangrene—considered to be referable to "hyperadrenalinemia"—with some cases of Raynaud's disease included. Apparently the mortality rate has now been kept low—2 deaths occurred in the "last 70 cases"—and some good effects are also said to have occurred.

Even in certain cases of cancer in man some promising results have been said to follow extirpation of one adrenal gland (89). In this connection it may be observed that noteworthy changes in the adrenal cortex occur on the production of experimental cancer in mice (8, 250). The recent flurry in clinical circles which has been evoked by the Coffey and Humber treatment of cancer by an extract of adrenal cortex from sheep may also be mentioned (57). Several cases of carcinoma (one also of sarcoma) have been treated, and in all cases studied it is reported that softening and liquefaction of the cancerous mass, usually within 24 to 48 hours after the first dose of extract, has occurred. In some instances recovery appears to have taken place, and the results are considered "quite promising" but still in the experimental stage.

The serious hazards which attend even unilateral adrenal removal have been considered in a previous section of this paper, and the forceful criticism which has been offered by Rogoff (224) has been mentioned. It does seem most desirable that at least a far better understanding of adrenal function (in truth but little of it is known at present) should be attained before operative interference with the highly important cortical tissue is allowed consideration. Stewart has made the assertion (256) that "probably nine-tenths of the medical profession are completely ignorant of the physiology of the adrenal bodies." Whether this be so or not, one is led devoutly to wish that the noblest ideals of the profession, which have been so well conceived and held aloft for the surgeon's gaze by Horsley (129), may have even as wide a propagation as the Gospel itself.

Theories of adrenal function. In the past decade and particularly within the past few years there has emerged from a welter of experimental evidence and many discussions a partial understanding at least of medulliadrenal activities in the animal economy. Reference to this phase of the subject has been made in a previous section. That the

very meagre knowledge of cortico-adrenal function does not lend itself at present even to rational theorizing is however all too evident. A number of hypothetical considerations which have been advanced in recent years have an element of freshness about them but otherwise little saving grace.

In a staid British journal it has been averred by one writer that the adrenal cortex plays a part in fat and calcium metabolism, stimulates the thymus and controls the gonads, whereas the whole gland is said to excite the thyroid and regulate hemoglobin degradation (126)! Another has cogitated that "the brain of the vegetative nervous system" is possibly represented by one part (evidently the medulla) of the adrenal mechanism (71). And in this breath appropriate allusion may also be given to the intriguing "self-control and inhibition" theory of adrenal behavior, which occupies a goodly part of the considerations in a recent monograph by Cramer (70a).

A theory which considers the involvement of the parathyroids as well as the adrenals in certain pressor responses has been put forward by Vincent and Thompson (293). These workers have also made the interesting observation that a substance which is essential for carrying on the normal movements of respiration is secreted by the adrenal cortex. It is said to pass through neighboring lymph glands and into the veins by way of the thoracic and right lymphatic ducts. Decerebrate cats were observed to succumb very rapidly if the adrenal glands or the lymphatics were excluded, and intravenous injections of fresh adrenal extract, given when respiration had ceased completely, restored normal breathing in two to three minutes. Adrenalin injections were found of no avail. It was concluded by these investigators that a respiratory autacoid, which they designated "pneumin," is elaborated by the cortico-adrenal tissue.

That decerebrate and bilaterally adrenalectomized animals may survive for considerable periods without respiratory failure supervening has, however, been frequently observed by other experimenters (44). In disagreement also with Vincent and Thompson, recent investigations by other workers have shown that no differences in respiration can be noted between normal and adrenalectomized decerebrate cats (90).

The possibility that medullary and cortical activities may be related has been widely debated, and is given consideration above. Chiefly it appears that influences on carbohydrate metabolism may be effected through both tissues, although all the evidence thus far has been inconclusive. A recent paper by Kahn and Münzer (149) postulates

that changes which are produced in both the cortex and the medulla on insulin injection and on splanchnic stimulation again suggest the functional duality of both parts of the gland. Cramer (70a) remarks that it would be difficult to understand how the medulla could ever be stimulated to increased activity without participation also of the cortex. The latter he considered might function alone, but the medullary tissue could not function independently of the cortex. The particularly intimate arrangement of the medullary and cortical vasculature has been reëmphasized by Cramer in connection with the foregoing.

A long list of different points is arrayed in a recent medical volume (190) in support of the contention that the adrenal cortex is closely connected with the sex glands—one theory about which there is said to be "little doubt." Marine and Baumann (198) consider that all the manifestations of adrenalectomy which have been thus far observed are "the individual details of a more fundamental and as yet unknown disturbance in nutrition in which the sympathetic nervous system is primarily involved."

Because of the high variability in weight of the adrenals it has been suggested by Boycott and Kellaway (28) that form and function in this case are less closely associated than usual. Compensatory regenerative growth, it is observed in general with the endocrine organs, is less than that found in other viscera. That excessive activity of the adrenals may be harmful to the organism has nevertheless been considered likely under certain circumstances by many authors.

Banting and Gairns (14) have remarked that the fact that histamine is thirty times more toxic after adrenalectomy suggests that a poison which is protein-like in nature accumulates in the body after the operation. It would scarcely be profitable here, however, to delve into the already much-discussed detoxication theory of adrenal function. The accumulation of toxin bodies after adrenal removal is apparent, but that this probably represents a by-product of the condition and supervenes chiefly in the later phases of adrenal insufficiency is also apparently the case. Experiments with the new cortical extract of Swingle may, it is fervently to be hoped, shed considerable light on the function of one of the most important tissues in the body.

CONCLUSIONS

In jotting down a rather disjointed story it has come to mind that perhaps it is the policy of the Editorial Board to offer one rather speculative review for adjudication each year: if so, then this offering will

have fulfilled at least that consideration. To attempt to tack on conclusions after having gone through the highways and byways of a seething mass of literature that may be said to have led to no very definite issues is also no sinecure. Some general observations and the results that have led up to the development in certain investigators' hands of a very potent cortical extract may nevertheless be given mention.

Under ordinary conditions all animals from which the cortico-adrenal tissues have been completely removed die within a week or two after operation. This appears true of primates and of widely-different species of wild and domestic mammals, of birds, reptiles, amphibia, and fishes. Symptoms are not usually evident for some days, although experiment reveals many functional deficiencies in such operated animals.

Within a few days after operation less activity is often shown, and the arterial pressure and blood sugar may show decreases; there is a tendency towards increased concentration of blood, and the blood urea and non-protein nitrogen are found to be increased. These conditions at least are incipient to and are often observed before the terminal symptoms develop. An increase in the serum calcium and reduction in blood chlorides also occurs; acid intoxication has been stressed by some observers. There is usually a considerable diminution in liver glycogen, and the blood sugar is often notably decreased.

Anorexia and other gastro-intestinal disturbances are early indications of oncoming dissolution; muscular weakness gradually develops and is followed frequently by convulsions, coma and death, usually within one or two days of the obvious appearances of sickness. A high protein diet is said to hasten death.

Animals (dogs) which are pregnant or in heat at the time of adrenal removal may live a few weeks beyond the normal limits of survival. A hibernating species (the marmot) survives for long periods when operated on during the winter season, but invariably perishes with the arrival of spring; in summer, death occurs a few days after operation. In some animals, transplants of adrenal cortex exert a protective function. The presence of accessory tissues in the rat and rabbit allows indefinitely long survival in these forms.

Administration of large amounts of physiological solutions (saline, etc.) tends to increase life up to a week or so longer than normal. The injection of glucose, or doses of adrenalin, gives only temporary relief of symptoms and prolongs life a day or so at best. A host of investigators have attempted to prolong the life of adrenalectomized animals by the use of adrenal extracts. Some slight indications of success have

attended the work of Rogoff and Stewart, and of Hartman and his collaborators.

Preliminary announcements of very important experiments which have been carried out by Swingle and Pfiffner indicate that they have eventually succeeded in retaining the cortical hormone in their extracts. All cats from which they have removed both adrenal glands can now be kept alive and in perfect health for periods up to 100 days by giving daily injections of the material. At the end of this period the injections have been withdrawn, and death of the animal then rapidly follows. Recovery of animals which have been allowed to develop severe symptoms of adrenal insufficiency can be effected in a few days with large doses of the extract. Adrenalin has not, however, been entirely separated from the material. These experiments apparently usher in a new era in investigations on the adrenal glands, and details of the work are keenly anticipated.

Post-mortem observations on animals which have died from adrenal insufficiency have emphasized the hemorrhagic or atrophic conditions found almost invariably in the pancreas. Gastro-intestinal ulcerations, lymphoid hyperplasia and lipoid nephrosis are also commonly observed pathological changes.

There appears incontrovertible evidence that it is the cortico-adrenal tissue *per se* which is absolutely essential to life. There are also many indications that the cortex is concerned with the storage and utilization of carbohydrates, or possibly with some phases of protein metabolism. Evidence at present indicates that the former is the more likely function.

About 10 per cent of the cortical tissue in the body is ordinarily sufficient to retain life under quiet routine conditions, but not without jeopardy. It may yet appear that the anatomically companionate cortical and medullary portions of the gland possess functional relationships.

It has been overwhelmingly made clear that medulliadrenal secretion is intimately and particularly concerned in adjusting and reinforcing bodily mechanisms in times of demand. That the chromaffin tissues can be spared without obviously endangering life yet with some detriment to the organism also appears well proven. Medulliadrenal insufficiency possibly finds mitigation in the vicarious activity of the sympathetic nervous system. Nevertheless the whole sympathico-medulliadrenal mechanism may be ablated without fatal result.

Addison's disease appears to be more particularly referable to cortico-

adrenal deficiency. It has not yet been shown, however, that regressive changes in the medullary tissues do not play a part in the etiology of the disease.

BIBLIOGRAPHY

(1) Abel, J. J. 1927. Science, lxvi, 307, 337.
(2) Abelous and Langlois. 1892. Arch. de Physiol., 269.
(3) Addison, T. 1849. London Med. Gaz., xliii, 517.
(4) Addison, T. 1855. On the constitutional and local effects of disease of the supra-renal capsules.
(5) Alvarez, W. C. et al. 1929. Amer. Journ. Physiol., xc, 631.
(6) Anrep, G. V. and I. deB. Daly. 1925. Proc. Roy. Soc., B, xcvii, 450.
(7) Aoki, M. 1927. Journ. Biol. Chem. (Tokyo), vii, 405.
(8) Arloing, F., A. Josserand and J. Charachon. 1929. Compt. rend. soc. biol., ci, 646.
(9) Artundo, A. 1927. Compt. rend. soc. biol., xcvii, 411.
(10) Artundo, A. 1927. Rev. soc. arg. biol., iii, 29.
(11) Aub, J. C., E. M. Bright and J. Uridil. 1922. Amer. Journ. Physiol., lxi, 300.
(12) Aufrecht and Diesing. 1909. Centralbl. f.d. ges. Physiol., iv, 369.
(13) Banting, F. G. and M. D. Finn. 1928. Amer. Journ. Physiol., lxxxvi, 43.
(14) Banting, F. G. and S. Gairns. 1926. Amer. Journ. Physiol., lxxvii, 100.
(15) Barbour, H. G. and R. W. Frankmann. 1927. Amer. Journ. Physiol., lxxxiii, 171.
(16) Barbour, H. G. and W. F. Hamilton. 1925. Proc. Soc. Exp. Biol. Med., xxii, 480.
(16a) Barker, N. W. 1929. Proc. Staff Meet., Mayo Clinic, iv, 91.
(17) Baschmakoff, W. J. 1923. Pflüger's Arch., cc., 379.
(18) Baumann, E. J. and O. M. Holly. 1923. Journ. Biol. Chem., lv, 457.
(19) Baumann, E. J. and S. Kurland. 1927. Journ. Biol. Chem., lxxi, 281.
(20) Belding, D. L. and L. C. Wyman. 1926. Amer. Journ. Physiol., lxxviii, 50.
(21) Benedict, F. G. and M. D. Finn. 1928. Amer. Journ. Physiol., lxxxvi, 59.
(22) Biasotti, A. 1927. Compt. rend. soc. biol., xcvii, 598.
(23) Biedl, A. 1913. Innere Sekretion. Berlin.
(24) Binet, L. and A. Giroud. 1928. Compt. rend. soc. biol., xcviii, 434.
(25) Blanchetière, A. and L. Binet. 1926. Compt. rend. soc. biol., xcv, 621.
(26) Boggild, D. H. 1925. Act. Path. Mic. Scand., ii, H. I, 68.
(27) Boinet, E. 1895. Compt. rend. soc. biol., xlvii, 162.
(28) Boycott, A. E. and C. H. Kellaway. 1924. Journ. Path. and Bact., xxvii, 171.
(29) Brenner, O. 1928. Quart. Journ. Med., xxii, 121.
(30) Bright, R. and T. Addison. 1839. Elements of practice of medicine. vol. I.
(31) Britton, S. W. 1928. Amer. Journ. Physiol., lxxxiv, 119.
(32) Britton, S. W. 1928. Ibid., lxxxvi, 340.

(33) Britton, S. W. 1930. Amer. Journ. Physiol., xciv, 686.
(34) Britton, S. W. Unpublished observations.
(35) Britton, S. W., E. M. K. Geiling and H. O. Calvery. 1928. Amer. Journ. Physiol., lxxxiv, 141.
(35a) Britton, S. W., A. Hinson and W. H. Hall. 1930. Amer. Journ., Physiol., xciii, 473.
(36) Brown, L. 1923. The sympathetic nervous system and disease.
(37) Brown-Sequard. 1892. Compt. rend. soc. biol., xliv, 410.
(38) Busch, F. C., T. M. Leonard and T. Wright. 1908. Journ. Amer. Med. Assoc., li, 640.
(39) Campos, F. A. de M., W. B. Cannon, H. Lundin and T. T. Walker. 1929. Amer. Journ. Physiol., lxxxvii, 680.
(40) Cannon, W. B. 1914. Amer. Journ. Physiol., xxxiii, 356.
(41) Cannon, W. B. 1928. Ergerbn. d. Physiol., xxvii, 380.
(42) Cannon, W. B. 1929. Bodily changes in pain, hunger, fear and rage. 2nd ed., New York.
(43) Cannon, W. B. 1930. Endocrinol., vi, 24.
(44) Cannon, W. B. and S .W. Britton. 1925. Amer. Journ. Physiol., lxxii, 283.
(45) Cannon, W. B. and S. W. Britton. 1927. Amer. Journ. Physiol., lxxix, 433.
(46) Cannon, W. B., H. F. Newton, E. M. Bright, V. Menkin and R. M. Moore. 1929. Amer. Journ. Physiol., lxxxix, 84.
(47) Cannon, W. B., and D. de la Paz. 1911. Amer. Journ. Physiol., xxviii, 64.
(48) Cannon, W. B., A. Querido, S. W. Britton and E. M. Bright. 1927. Amer. Journ. Physiol., lxxix, 466.
(49) Cannon, W. B., A. T. Shohl and W. S. Wright. 1911. Amer. Journ. Physiol., xxix, 280.
(50) Castaldi, L. 1924. Rend. d. R. Acc. d. Lincei, xxxiii, 94.
(51) Chahovitch, X, V. Arnovljevitch and M. Vichnjitch. 1928. Soc. Biol., xcviii, 511.
(52) Chamberlain, E. N. 1928. Journ. Physiol., lxvi, 249.
(53) Chamberlain, E. N. 1930. Ibid., lxix, proc. vi.
(54) Chichester, F. E., A. G. Eaton and G. P. Thompson. 1929. Amer. Journ. Physiol., lxxxviii, 191.
(55) Charrin, A. and A. Gouillemonat. 1900. Compt. rend. soc. biol., lii, 211, 247.
(56) Clogne, R. 1924. Gynec. et Obs., x, 22.
(57) Coffey, W. B. and J. D. Humber. 1930. Journ. Amer. Med. Assoc., xciv, 359.
(58) Coombs, H. C. 1925. Amer. Journ. Physiol., lxxii, 200.
(59) Corey, E. L. 1928. Phys. Zoöl., i, 147; Proc. Soc. Exp. Biol. Med., xxv, 685.
(60) Corey, E. L. Unpublished observations.
(61) Cori, C. F. and G. T. Cori. 1927. Journ. Biol. Chem., lxxiv, 473.
(62) Cori, C. F. and G. T. Cori. 1928. Ibid., lxxix, 309.
(63) Cori, C. F. and G. T. Cori. 1929. Ibid., lxxxi, 389.
(64) Cori, C. F. and G. T. Cori. 1929. Ibid., lxxxiv, 683.
(65–6) Costa, A. C. da. 1929. Compt. rend. soc. biol., c, 517.
(67) Costantini, H. 1927. Bull. et mém. soc. nat. de chir., liii, 529.

(68) Courrier, R. 1926. Soc. Biol., xciv, 1386.
(69) Cramer, W. 1918. Journ. Physiol., lii, proc. viii.
(70) Cramer, W. 1926. Brit. Journ. Exp. Path., vii, 88.
(70a) Cramer, W. 1928. Fever, heat regulation, climate and the thyroid-adrenal apparatus. London.
(71) Crile, G. W. 1929. Surg. Gyn. Obs., xlviii, 371.
(72) Crivellari, C. A. 1926. Rev. Soc. arg. biol., ii, 448.
(73) Crowden, G. P. and M. G. Pearson. 1928. Journ. Physiol., lxv, proc. xxxii.
(74) Dale, H. H. 1929. Lancet, i, 1179.
(75) Donaldson, J. C. 1919. Amer. Journ. Anat., xxv, 291.
(76) Donath, J. 1914. Arch. f. exp. Path. u. Pharm., lxxvii, 1.
(77) Drabkin, D. L. and D. J. Edwards. 1924. Amer. Journ. Physiol., lxx, 273.
(78) Durante, L. 1912–13. Pathologica, v, 631.
(79) Durrant, E. P. 1924. Amer. Journ. Physiol., lxx, 344.
(80) Durrant, E. P. 1928. Amer. Journ. Physiol., lxxxv, 364.
(81) Eaton, A. G., W. M. Insko, G. P. Thompson and F. E. Chichester. 1929. Amer. Journ. Physiol., lxxxviii, 187.
(81a) Editorials in Journ. Amer. Med. Assoc., 1927, lxxxix, 1784; 1928, xc, 771; 1929, xciii, 1734.
(82) Elman, R. and P. Rothman. 1924. Johns Hopkins Hosp. Bull., xxxv; 64.
(83) Elliott, T. R. 1914. Journ. Physiol., xlix, 38.
(84) Elliott, T. R. and I. U. Tuckett. 1906. Journ. Physiol., xxxiv, 332.
(85) Estrada, O. P. 1923. Sem. Méd., xxxiii, 1653.
(86) Estrada, O. P. 1926. Rev. Soc. arg. biol., ii, 348.
(87) Evans, H. M. Personal communication.
(88) Finzi, O. 1913. Virchow's Arch., ccxiv, 413.
(89) Flörcken, H. 1927. Zeitschr. f. Kreb., xxiv, 465.
(90) Florey, H., A. Szent-Györgi and M. E. Florey. 1929. Journ. Physiol., lxvii, 343.
(91) Folin, O., W. Denis and W. G. Smillie. 1914. Journ. Biol. Chem., xvii, 519.
(92) Fujii, I. 1920. Tohoku Journ. Exper. Med., i, 38.
(93) Fujii, I. 1924. Ibid., v, 405.
(94) Gamble, J. L. and M. A. McIver. 1925. Proc. Soc. Exp. Biol. Med., xxii, 365.
(95) Gans, H. M. and H. H. Miley. 1927. Amer. Journ. Physiol., lxxxii, 1.
(96) Garrison, F. H. 1929. History of medicine. Philadelphia.
(97) Gayda, T. 1923. Arch. di Sci. Biol., iv, 93.
(98) Geiling, E. M. K., S. W. Britton and H. O. Calvery. 1929. Journ. Pharm. Exp. Therap., lxxxvi, 235.
(99) Gherardini, G. 1929. Endoc. e patol. costit., iv, 183.
(100) Gibelli, C. 1909. Path., i, 131.
(101) Giusti. 1921. Compt. rend. soc. biol., lxxxv, 30, 312.
(102) Goldzieher, M. A. 1928. Journ. Amer. Med. Assoc., xci, 2013.
(103) Goldzieher, M. A. 1928. Klin. Wochenschr., vii, 1124.
(104) Goldzieher, M. A. 1929. The adrenals. New York.

(105) Gonzalez, J. M. L. 1929. Rev. soc. arg. biol., v, 312.
(106) Gonzalez, J. M. L. 1929. Compt. rend. soc. biol., cii, 458.
(107) Goormaghtigh, N. and L. Elaut. 1925. Compt. rend. soc. biol., xci, 733.
(108) Gradinescu, A. V. 1913. Pflüger's Arch., clii, 187.
(109) Gray, H. 1924. Anatomy of the human body. New York.
(110) Griffith, F. R. et al. 1927. Amer. Journ. Physiol., lxxxi, 483.
(111) Gunn, F. D., C. F. Cori and F. A. Hartman. 1927. Proc. Soc. Biol. Med., xxv, 410.
(112) Gustafson, F. L. and F. G. Banting. 1928. Amer. Journ. Physiol., lxxxvi, 43.
(113) Haberer, von H. and O. Stoerk. 1918. Zeitschr. f. d. ges. exp. Med., vi, 1.
(114) Harding, V. J. 1925. Physiol. Rev., v, 279.
(115) Harrison, T. R., A. Blalock, C. Pilcher and C. P. Wilson. 1927. Amer. Journ. Physiol., lxxxiii, 284.
(116) Hartman, F. A. 1926. Proc. Soc. Exp. Biol. Med., xxiii, 467.
(117) Hartman, F. A., and K. A. Brownell, W. E. Hartman, G. A. Dean and C. G. MacArthur. 1928. Amer. Journ. Physiol., lxxxvi, 353.
(118) Hartman, F. A., F. R. Griffith and W. E. Hartman. 1928. Amer. Journ. Physiol., lxxxvi, 360.
(119) Hartman, F. A. and W. E. Hartman. 1923. Amer. Journ. Physiol., lxv, 623.
(120) Hartman, F. A., C. G. MacArthur, F. D. Gunn, W. E. Hartman and J. J. MacDonald. 1927. Amer. Journ. Physiol., lxxxi, 244.
(121) Hartman, F. A., C. G. MacArthur and W. E. Hartman. 1927. Proc. Soc. Exp. Biol. Med., xxv, 69.
(122) Hartman, F. A., H. A. McCordock and M. M. Loder. 1923. Amer. Journ. Physiol., lxiv, 1.
(123) Henderson, E. F. 1927. Anat. Rec., xxxvi, 69.
(124) Henry, F. P. 1913. In Ref. Handbook of Med. Sci., i, 114.
(125) Herring, P. T. 1920. Brit. Med. Journ., xi, 886.
(126) Hewer, E. E. 1922. Brit. Med. Journ., i, 138.
(127) Hirase, K. 1926. Pflüger's Arch., ccxii, 582.
(128) Honan, M. S. 1930. Amer. Journ. Anat., lxiv, 194.
(129) Horsley, J. S. 1929. Research in medical progress. St. Louis.
(130) Hoskins, R. G. 1922. Physiol. Rev., ii, 343.
(131) Hosoi, K., H. Ascanio and W. C. Alvarez. 1927. Proc. Staff Mtg. Mayo Clinic, iv, 211.
(132) Hou, H. C. 1929. Proc. Soc. Exp. Biol. Med., xxvi, 745.
(133) Houssay, B. A. and A. Artundo. 1929. Compt. rend. soc. biol., c, 127.
(134) Houssay, B. A. and J. T. Lewis. 1923. Amer. Journ. Physiol., lxiv, 512.
(135) Houssay, B. A. and E. A. Molinelli. 1926. Amer. Journ. Physiol., lxxvi, 538.
(136) Houssay, B. A. 1926. Rev. soc. arg. biol., ii, 117.
(137) Houssay, B. A. 1926. Compt. rend. soc. biol., xcv, 819.
(138) Howden, R. 1913. In Gray's Anatomy, Pt. v.
(139) Huth, E. 1929. Wien. klin. Wochenschr. xlii, 739.
(140) Izquierdo, J. J. 1928. Amer. Journ. Physiol., lxxxvi, 145.

(141) JAFFE, H. L. 1924. Journ. Exp. Med., xl, 325, 619.
(142) JAFFE, H. L. 1926. Amer. Journ. Physiol., lxxviii, 453.
(143) JAFFE, H. L. 1926. Amer. Journ. Path., ii, 421.
(144) JAFFE, H. L. 1927. Journ. Exp. Med., xlv, 587.
(145) JAFFE, H. L. 1927. Arch. Path. and Lab. Med., iii, 414.
(146) JAFFE, H. L. AND A. PLAVSKA. 1926. Proc. Soc. Exp. Biol. Med., xxiii, 528.
(147) JOELSON, J. J. AND E. SHORR. 1924. Arch. Int. Med., xxxiv, 841.
(148) KAHN, R. H. 1912. Pflüger's Arch., cxlvi, 578.
(149) KAHN, R. AND F. T. MUNZER. 1927. Pflüger's Arch., ccxvii, 521.
(150) KEENE, M. F. L. AND E. E. HEWER. 1927. Journ. Anat., lxi, 302.
(151) KELLAWAY, C. H. AND H. S. COWELL. 1923. Journ. Physiol., lvii, 82.
(152) KISCH, B. 1928. Pflüger's Arch., ccxix, 426.
(153) KODAMA, S. 1923. Tohoku Journ. Exp. Med., iv, 166.
(154) KOEHLER, A. E. 1928. Journ. Amer. Med. Assoc., xci, 1457.
(155) KOEHLER, A. E. 1929. Proc. Soc. Exp. Biol. Med., xxvi, 296.
(156) KOEHLER, A. E. AND L. EICHELBERGER. 1929. Amer. Journ. Physiol., xc, 417.
(157) KOEHLER, A. E. AND A. B. HASTINGS. 1929. Amer. Journ. Physiol., xc, 418.
(158) KOJIMA, T. 1929. Tohoku Journ. Exp. Med., xiii, 237.
(159) KUNTZ, A. 1929. The autonomic nervous system. Philadelphia.
(160) KUHL, J. 1927. Pflüger's Arch., ccxv, 277.
(170) KURIYAMA, S. 1918. Journ. Biol. Chem., xxxiv, 287.
(171) LAMSON, P. D. 1915. Journ. Pharm. Exp. Therap., vii, 169.
(172) LAWRENCE, C. H. AND A. W. ROWE. 1929. Endocrinol., xiii, 1.
(173) LEGRAND AND BIERENT. 1927. Compt. rend. soc. biol., xcvi, 291.
(174) LERICHE, R. AND P. STRICKER. 1929. Brit. Journ. Surg., xvi, 500.
(175) LESCHKE, E. 1928. Med. Klin., xxiv, 1268.
(176) LESCHKE, E. 1929. Verh. d. Berl. med. Ges., lix, 172.
(177) LEWIS, J. T. 1923. Amer. Journ. Physiol., lxiv, 503.
(178) LEWIS, J. T. 1923. Ibid., lxiv, 506.
(179) LEWIS, J. T. AND A. TORINO. 1927. Compt. rend. soc. biol., xcvi, 217.
(180) LOEPER, M., R. GARCIN AND A. LESURE. 1926. Compt. rend. soc. biol., xcii, 620.
(181) LOEWI, O. AND W. GETTWERT. 1914. Pflüger's Arch., clviii, 29.
(182) LONG, C. N. H. 1928. Journ. Biol. Chem., lxxvii, 563.
(183) LUCAS, G. W. H. 1926. Amer. Journ. Physiol., lxxvii, 114.
(184) LUMLEY, F. H. AND L. B. NICE. 1930. Amer. Journ. Physiol., xciii, 152.
(185) LURIE, M. 1928. Endocrinal., xii, 84.
(186) LUTZ, B. R. AND M. A. CASE. 1925. Amer. Journ. Physiol., lxxiii, 670.
(187) LUTZ, B. R. AND L. C. WYMAN. 1927. Journ. Exp. Zoöl., xlvii, 295.
(188) MACKAY, E. M. AND L. L. MACKAY. 1926. Journ. Exp. Med., xliii, 395.
(189) MACKAY, E. M. AND L. L. MACKAY. 1929. Jour. Pharm. Exp. Therap., xxxv, 67.
(190) MACLEOD, J. J. R. 1930. Physiology and biochemistry in modern medicine.
(191) MACLEOD, J. J. R. AND R. G. PEARCE. 1912. Amer. Journ. Physiol., xxix, 419.
(192) MACMAHON, H. E. AND R. L. ZWEMER. 1929. Amer. Journ. Path., v, 491.
(193) MANN, F. C. 1916. Journ. Exp. Med., xxiii, 203.

(194) Mann, F. C. 1916. Ibid., xxiv, 329.
(195) Maranon, G. 1925. Presse Med., xxxvi, 1021.
(196) Marine, D. and E. J. Baumann. 1922. Journ. Met. Res., ii, 1.
(197) Marine, D. and E. J. Baumann. 1922. Amer. Journ. Physiol., lxix, 353.
(198) Marine, D. and E. J. Baumann. 1927. Amer. Journ. Physiol., lxxxvi, 86.
(199) Marine, D., E. J. Baumann and A. Cipra. 1925. Amer. Journ. Physiol., lxxii, 248.
(200) Marmorston-Gottesman, J. and J. Gottesman. 1928. Journ. Exp. Med., xlvii, 503.
(201) Marshall, E. K. and D. M. Davis. 1916. Journ. Pharm. Exp. Therap., viii, 525.
(202) Marval, L. de. 1926. Compt. rend. soc. biol., xcv, 1087.
(203) Mira, F. and J. Fontes. 1928. Compt. rend. soc. biol., xcviii, 987.
(204) Mira F. and J. Fontes. 1929. Compt. rend. soc. biol., c, 602.
(205) Moore, R. A. 1928. Endocrinol., xxii, 800.
(206) Moore, B. and C. O. Purinton. 1900. Amer. Journ. Physiol., iv, 51.
(207) Moore, B. and C. O. Purinton. 1901. Ibid., v, 182.
(208) Morris. 1925. Human anatomy.
(209) Neuman, K. O. 1912. Journ. Physiol., xlv, 188.
(210) Obré, A. 1923. Compt. rend. soc. biol., lxxxviii, 585.
(211) Oldberg, E. 1929. Amer. Journ. Physiol., xci, 275.
(212) Oppel, V. A. 1928. Ann. Surg., lxxxvii, 801.
(213) Orr, T. G. and R. L. Haden. 1929. Journ. Exp. Med., xlix, 525.
(214) Perla, D. and J. M. Gottesman. 1928. Amer. Journ. Physiol., lxxxix, 152.
(215) Pfiffner, J. J. and W. W. Swingle. 1929. Anat. Rec., xliv, 225.
(216) Putschkow, N. W. and W. W. Krassnow. 1928. Pflüger's Arch., ccxx, 44.
(217) Pybus, F. C. 1924. Lancet, ii, 550.
(218) Randles, F. S. and A. Knudson. 1928. Journ. Biol. Chem., lxxvi, 89.
(219) Riddle, O. 1929. Journ. Amer. Med. Assoc., xcii, 943.
(220) Riddle, O. and W. S. Fisher. 1925. Amer. Journ. Physiol., lxxii, 464.
(221) Riolanus. 1629. Les Oeuvres Anatomiques. Paris.
(222) Rivers, W. H. R. 1916. Lancet, i, 59, 117.
(223) Rogoff, J. M. 1925. Journ. Pharm. Exp. Therap., xxv, 155.
(224) Rogoff, J. M. 1928. Ann. Surg., lxxxvii, 959.
(225) Rogoff, J. M. 1929. Endocrinol. v, 256.
(226) Rogoff, J. M. and R. Dominguez. 1924. Journ. Met. Res., vi, 141.
(227) Rogoff, J. M. and R. Dominguez. 1927. Amer. Journ. Physiol., lxxxiii, 84.
(228) Rogoff, J. M. and G. N. Stewart. 1926. Amer. Journ. Physiol.. lxxviii, 683.
(229) Rogoff, J. M. and G. N. Stewart. 1926. Ibid., 711.
(230) Rogoff, J. M. and G. N. Stewart. 1927. Ibid., lxxix, 508.
(231) Rogoff, J. M. and G. N. Stewart. 1927. Science, lxvi, 327.
(232) Rogoff, J. M. and G. N. Stewart. 1928. Amer. Journ. Physiol., lxxxiv, 649.
(233) Rogoff, J. M. and G. N. Stewart. 1928. Ibid., 660.
(234) Rogoff, J. M. and G. N. Stewart. 1928. Ibid., lxxxvi, 20.

(235) Rogoff, J. M. and G. N. Stewart. 1928. Ibid., 25.
(236) Rogoff, J. M. and G. N. Stewart. 1929. Ibid., lxxxviii, 162.
(237) Rogoff, J. M. and G. N. Stewart. 1929. Ibid., xc, 397.
(238) Rogoff, J. M. and G. N. Stewart. 1929. Ibid., xci, 294.
(239) Rogoff, J. M. and G. N. Stewart. 1929. Journ. Amer. Med. Assoc., xcii, 1569.
(240) Rowntree, L. G. 1924. Journ. Pharm. Exp. Therap., xxiii, 135.
(241) Saito, S. 1929. Tohoku Journ. Exp. Med., xii, 254.
(242) Satake, Y. and T. Kojima. 1929. Amer. Journ. Physiol., xc, 505.
(243) Scammon, R. E. 1926. Proc. Soc. Exp. Biol. Med., xxiii, 809.
(244) Schafer, E. S. 1898. Textbook of physiology, 1.
(245) Schafer, E. S. 1924. The endocrine organs. Pt. I. London.
(246) Scott, W. J. M. 1928. Journ. Exp. Med., xlvii, 185.
(247) Snell, A. M. and L. G. Rowntree. 1929. Ann. Int. Med., iii, 6.
(248) Snyder, F. F. and F. M. Hoskins. 1927. Anat. Rec., xxxv, 23.
(249) Soddu, L. 1899. Sperimentale, 52.
(250) Sokoloff, B. 1929. Compt. rend. soc. biol., ci, 264.
(251) Spohr, C. and R. A. Moore. 1927. Journ. Lab. Clin. Med., xii, 438.
(252) Stefl, J. 1928. Compt. rend. soc. biol., xcix, 985.
(253) Stewart, G. N. 1914. Trans. Int. Cong. Med., Sec. III.
(254) Stewart, G. N. 1921. Endocrinol, v, 283.
(255) Stewart, G. N. 1924. Physiol Rev., iv, 463.
(256) Stewart, G. N. 1929. Arch. Int. Med., xliii, 733.
(257) Stewart, G. N. and J. M. Rogoff. 1917. Journ. Pharm. Exp. Therap., x, 1.
(258) Stewart, G. N. and J. M. Rogoff. 1918. Amer. Journ. Physiol., xlvi, 90.
(259) Stewart, G. N. and J. M. Rogoff. 1919. Ibid., xlviii, 397.
(260) Stewart, G. N. and J. M. Rogoff. 1922. Ibid., lxii, 93.
(261) Stewart, G. N. and J. M. Rogoff. 1922. Journ. Pharm. Exp. Therap., xix, 87, 97.
(261a) Stewart, G. N. and J. M. Rogoff. 1925. Proc. Soc. Exp. Biol. Med., xxii, 394.
(262) Stewart, G. N. and J. M. Rogoff. 1926. Amer. Journ. Physiol., lxxvii, 683.
(262a) Stewart, G. N. and J. M. Rogoff. 1929. Ibid., xci, 254.
(263) Stewart, H. A. 1913. Reported by MacCallum, Int. Cong. Med. (Lon.), Sec. III, 173.
(264) Still, K. S. and A. J. Carlson. 1929. Amer. Journ. Physiol., lxxxix, 34.
(265) Stilling, H. 1888. Rev. Méd., viii, 459.
(266) Strehl, H. and O. Weiss. 1901. Pflüger's Arch., lxxxvi, 107.
(267) Stulz, E. and P. Stricker. 1927. Rev. de chir., lxv, 196.
(268) Sugawara, T., M. Watanabe and S. Saito. 1926. Tohoku Journ. Exp. Med., vii, 1.
(269) Sun, T. P. 1929. Endocrinol., xiii, 549.
(270) Swingle, W. W. 1927. Amer. Nat., lxi, 132.
(271) Swingle, W. W. 1927. Amer. Journ. Physiol., lxxix, 666.
(272) Swingle, W. W. 1928. Ibid., lxxxvi, 450.
(273) Swingle, W. W. and A. J. Eisenman. 1927. Amer. Journ. Physiol., lxxix, 679.

(274) SWINGLE, W. W. AND J. J. PFIFFNER. 1929. Anat. Rec., xliv, 225.
(275) SWINGLE, W. W. AND J. J. PFIFFNER. 1930. Science, lxxi, 321.
(276) SWINGLE, W. W. AND J. J. PFIFFNER. 1930. Ibid., 489.
(276a) SWINGLE, W. W. AND J. J. PFIFFNER. 1930. Personal communication.
(277) SWINGLE, W. W. AND W. F. WENNER. 1927. Proc. Soc. Exp. Biol. Med., xxv, 169.
(278) SWINGLE, W. W. AND W. F. WENNER. 1928. Physiol. Zoöl., i, 37.
(279) SZENT-GYÖRGYI, A. V. 1927. Biol. Zeitschr., clxxxi, 433.
(280) SZENT-GYÖRGYI, A. V. 1929. Amer. Journ. Physiol., xc, 536.
(281) TACHI, H. 1928. Tohoku Journ. Exp. Med., x, 307.
(282) TAMMANN, H. 1924. Beit. z. path. Anat. u. z. allg. Path., lxxiii, 307.
(283) TAYLOR, N. B. AND W. R. CAVEN. 1927. Amer. Journ. Physiol., lxxxi, 511.
(284) TIGERSTEDT, C. 1926. Skand. Arch. f. Physiol., xlviii, 138.
(285) TOURNADE, A. AND M. CHABROL. 1925. Compt. rend. soc. biol., xcii, 418.
(286) UNDERHILL, F. P., F. J. PETERMAN AND A. SPERANDEO. 1929. Amer. Journ. Physiol., xc, 76.
(287) UNVERRICHT. 1926. Deutsch. med. Wochenschr., lii, 1298.
(288) VIALE, G. 1927. Rev. soc. arg. biol., iii, 725.
(289) VIALE, G., S. M. MEUSCHLOSZ AND E. TURKATTI. 1927. Rev. soc. arg. biol., iii, 171.
(290) VELICH, A. 1906. Virchow's Arch., 184.
(291) VINCENT, S. 1924. Internal secretion and the ductless glands. London.
(292) VINCENT, S. AND F. R. CURTIS. 1927. Journ. Anat., lxii, 110.
(293) VINCENT, S. AND J. H. THOMPSON. 1928. Journ. Physiol., lxvi, 449.
(294) WATANABE, M. AND H. SAITO. 1928. Tohoku Journ. Exp. Med., xi, 433.
(295) WEYMANN, M. D. 1922. Anat. Rec., xxiv, 299.
(296) WHEELER, T. D. AND S. VINCENT. 1917. Trans. Roy. Soc. Con., xi, 125.
(297) WIEMAN, H. L. 1920. Anat. Rec., xix, 269.
(298) WIESEL. 1903. Zeitschr. f. Heil., xxiv.
(299) WILKS AND DALDY. 1868. A collection of published writings of the late Thos. Addison. London.
(300) WISLOCKI, G. B. AND S. J. CROWE. 1924. Johns Hopkins Hosp. Bull., xxxv, 187.
(301) WOODHOUSE, D. L. 1928. Biol. Journ., xxii, 1087.
(302) WYMAN, L. C. 1928. Amer. Journ. Physiol., lxxxvii, 29.
(303) WYMAN, L. C. 1928. Ibid., 42.
(304) WYMAN, L. C. 1928. Ibid., lxxxvi, 528.
(305) WYMAN, L. C. 1929. Ibid., lxxxix, 356.
(306) WYMAN, L. C. 1930. Personal communications.
(307) WYMAN, L. C. AND C. T. SUDEN. 1929. Amer. Journ. Physiol., lxxxix, 362.
(308) WYMAN, L. C. AND B. S. WALKER. 1929. Amer. Journ. Physiol., lxxxix, 215.
(309) YONKMAN, F. F. 1927. Proc. Soc. Exp. Biol. Med., xxiv, 786.
(310) ZWEMER, R. L. 1927. Amer. Journ. Physiol., lxxix, 641, 658.
(311) ZWEMER, R. L. AND C. LYONS. 1928. Amer. Journ. Physiol., lxxvi, 545.

PHYSIOLOGICAL REVIEWS

Index to Volumes I to X

A

Absorption from intestine, mechanism of, 1921, I, 421.
Acid-base balance of blood, physiological regulation of, 1925, V, 13.
equilibrium in body, 1923, III, 295.
equilibrium, mineral metabolism and, 1923, III, 509.
Acclimatisation to high altitudes, 1927, VII, 363.
Adrenal bodies, relation of, to metabolism, 1924, IV, 163.
Adrenal insufficiency and related considerations, 1930, X, 617.
Adrenalectomy and relation of adrenal bodies to metabolism, 1924, IV, 163.
Adrenals, relation of, to circulation, 1922, II, 343.
Adrian, E. D. The mechanism of the sense organs, 1930, X, 336.
Adsorption, 1921, I, 553.
Aerobic oxidases, 1928, VIII, 245.
Afferent paths for visceral reflexes, 1921, I, 477.
Allen, E. and **E. A. Doisy.** Ovarian and placental hormones, 1927, VII, 600.
Alsberg, C. L. *See* VAN DE SANDE-BAKHUYZEN and ALSBERG, 1927, VII, 151.
Altitude, physiological effects of, 1921, I, 631.
Altitudes, high, acclimatization to, 1927, VII, 363.
Alvarez, W. C. Intestinal autointoxication, 1924, IV, 352.
Anaphylaxis, 1921, I, 44.
anti-, and desensitization, 1923, III, 240.
Anhydremia, 1923, III, 275.
Anrep, G. V. The regulation of the coronary circulation, 1926, VI, 596.
Anson, M. L. and **A. E. Mirsky.** Hemoglobin, the heme pigments and cellular respiration, 1930, X, 506.
Anti-anaphylaxis and desensitization, 1923, III, 240.
Appetites, perverted, 1925, V, 336.
Arsenicals, related, pharmacology of arsphenamine and, 1925, V, 63.
Arsphenamine (salvarsan) and related arsenicals, 1925, V, 63.
Arterial hypertension and hypotension, 1927, VII, 431.
Arteriosclerosis, 1922, II, 70.
Asdell, S. A. The growth and function of the corpus luteum, 1928, VIII, 313.
Atmospheric conditions, industrial fatigue and, 1928, VIII, 130.
Atrophy, autolysis and, 1922, II, 415.
Auricular fibrillation, 1924, IV, 215.
Autointoxication, intestinal, 1924, IV, 352.
Autolysis and atrophy, 1922, II, 415.
Autonomic system, pharmacology of, 1922, II, 479.

B

Baas-Becking, L. G. M. and G. S. Parks. Energy relations in the metabolism of autotrophic bacteria, 1927, VII, 85.
Babkin, B. P. The digestive work of the stomach, 1928, VIII, 365.
Bacteria, autotrophic, metabolism of, 1927, VII, 85.
local resistance and local immunity to, 1924, IV, 191.
Bacteria metabolism, 1923, III, 438.
Bacteriophage, 1925, V, 95.
Barbour, H. G. The heat-regulating mechanism of the body, 1921, I, 295.
Barcroft, J. The significance of hemoglobin, 1924, IV, 329.
The significance of hemoglobin in submammalian forms of life, 1925, V, 596.
Basal metabolism, 1924, IV, 69.
of children, 1925, V, 477.
Bazett, H. C. Physiological responses to heat, 1927, VII, 531.
Bile, extra-hepatic functions of, 1927, VII, 129.
origin and significance of constituents of, 1922, II, 440.
Bile pigment, formation of, 1925, V, 182.
Biological assay, errors of, 1930, X, 146.
Bioluminescence, recent advances in, 1924, IV, 639.
Bismuth, absorption, distribution and excretion of, 1930, X, 221.
Blood, carbon dioxide carriers of, 1912, I, 141.
cells, origin of, 1922, II, 38.
cells, relation of, to connective tissues and endothelium, 1924, IV, 533.
chemical changes in, 1924, IV, 274.
corpuscles, red, destruction of, 1923, III, 75.
non-protein nitrogen of, 1922, II, 460.
physiological regulation of acid-base balance of, 1925, V, 131.
pressures in man, 1925, V, 303.
sugar, 1921, I, 208.
sugar and diabetes, 1926, VI, 630.
suspension stability of, 1929, IX, 241.
volume and its regulation, 1921, I, 177.
Bloor, W. R. Fat transport in the animal body, 1922, II, 92.
Body fluids and tissues, paleochemistry of, 1926, VI, 316.
Bone marrow, 1928, VIII, 191.
Boothby, W. M. and I. Sandiford. Basal metabolism, 1924, IV, 69.
Borsook, H. *See* Wasteneys and Borsook, 1930, X, 110.
Bradley, H. C. Autolysis and atrophy, 1922, II, 415.
Britton, S. W. Adrenal insufficiency and related considerations, 1930, X, 617.
Bronchi and lungs, musculature of, 1929, IX, 1.
Bull, C. G. Bacteriophage, 1925, V, 95.
Bunting, C. H. The leukocytes, 1922, II, 505.
Burn, J. H. The errors of biological assay, 1930, X, 146.

C

Calcium metabolism, 1928, VIII, 283.
Cannon, W. B. Organization for physiological homeostasis, 1929, IX, 399.

Capillaries and venules, functional activity of, 1921, I, 112.
Carbohydrates, intermediary metabolism of, 1923, III, 394.
Carbon dioxide carriers of blood, 1921, I, 141.
Cardiac tonus, 1927, VII, 259.
Caries, dental, 1924, IV, 564.
Carlson, A. J. The secretion of gastric juice in health and disease, 1923, III, 1.
Carrel, A. Tissue culture and cell physiology, 1924, IV, 1.
Cathcart, E. P. The influence of muscle work on protein metabolism, 1925, V, 225.
Cell physiology, tissue culture and, 1924, IV, 1.
Cells of blood, origin of, 1922, II, 38.
Cellular immunity: congenital and acquired tolerance to non-protein substances, 1923, III, 41.
Cellular respiration, hemoglobin, the heme pigments and, 1930, X, 506.
Cerebellum, physiology of, 1926, VI, 124.
Cerebral localization, 1929, IX, 462.
Cerebrospinal fluid, 1922, II, 171.
Chemical changes in blood and their clinical significance, 1924, IV, 274.
Chemistry of degradation of protein nitrogen, 1930, X, 1.
physical, of proteins, 1925, V, 349.
Chemotherapy, 1923, III, 359.
Children, basal metabolism of, 1925, V, 477.
Chronaxie, 1928, VIII, 501.
Circulation, coronary, regulation of, 1926, VI, 596.
pulmonary, regulation of, 1921, I, 239.
relation of adrenals to, 1922, II, 343.
Clark, J. H. The physiological action of light, 1922, II, 277.
Climate, tropical, physiological effects of, 1927, VII, 320.
Cobb, S. Review on the tonus of skeletal muscle, 1925, V, 518.
Cohn, E. J. The physical chemistry of the proteins, 1925, V, 349.
Conduction, excitation and, in protoplasm, 1922, II, 1.
Connective tissue and endothelium, relation of blood cells to, 1924, IV, 533.
Contraction, muscular, 1922, II, 310.
Contractures of skeletal muscle, 1930, X, 35.
Corner, G. W. Oestrus, ovulation and menstruation, 1923, III, 457.
Coronary circulation, regulation of, 1926, VI, 596.
Corpus luteum, growth and function of, 1928, VIII, 313.
Corpuscles, red, of blood, destruction of, 1923, III, 75.
Creatine and creatinine, physiology of, 1922, II, 586.
Creatinine, creatinine and, physiology of, 1922, II, 586.
Cunningham, R. S. The physiology of the serous membranes, 1926, VI, 242.

D

Dakin, H. D. Physiological oxidations, 1921, I, 394.
Dale, H. H. Chemotherapy, 1923, III, 359.
Davis, H. The conduction of the nerve impulse, 1926, VI, 547.
Dental caries, etiology of, 1924, IV, 564.
Desensitization, anti-anaphylaxis and, 1923, III, 240.

Detlefsen, J. A. The inheritance of acquired characters, 1925, V, 244.
Diabetes, blood sugar and, 1926, VI, 630.
phlorhizin, 1927, VII, 385.
Diet and sterility, 1926, VI, 485.
influence of, on structure of teeth, 1928, VIII, 545.
milk secretion and, 1922, II, 204.
Digestion, intracellular, 1922, II, 552.
rôle of hormones in, 1930, X, 282.
work of, in stomach, 1928, VIII, 365.
Doan, C. A. The transfusion problem, 1927, VII, 1.
Doisy, E. A. *See* ALLEN and DOISY, 1927, VII, 600.
Donnan equilibrium, proteins and, 1924, IV, 505.
Dragstedt, L. R. The physiology of the parathyroid glands, 1927, VII, 499.
Dunn, H. L. Application of statistical methods in physiology, 1929, IX, 275.

E

Edema, 1925, V, 618.
Egg, developing, metabolism of, 1925, V, 1.
Eggleton, P. The position of phosphorus in the chemical mechanism of muscular contraction, 1929, IX, 432.
Electrogram and electrocardiogram, T wave of, 1928, VIII, 447.
Embryonic development, genetics and, 1923, III, 603.
Endothelium, relation of blood cells to connective tissues and, 1924, IV, 533.
Energy relations in metabolism of autotrophic bacteria, 1927, VII, 85.
Enzymatic synthesis of protein, 1930, X, 110.
Enzymes and anti-enzymes concerned in intracellular digestion, 1922, II, 552.
Erlanger, J. Blood volume and its regulation, 1921, I, 177.
Erythrocytes, regeneration of hemoglobin and, 1929, IX, 666.
Evans, C. L. The physiology of plain muscle, 1926, VI, 358.
Excitation and conduction in protoplasm, 1922, II, 1.
Eye, photo-electric currents in, 1921, I, 84.
Eyster, J. A. E. Venous pressure and its clinical applications, 1926, VI, 281.
Eyster, J. A. E. and **W. J. Meek.** The origin and conduction of the heart beat, 1921, I, 1.

F

Fåhraeus, R. The suspension stability of the blood, 1929, IX, 241.
Fat transport in animal body, 1922, II, 92.
Fatigue, industrial, in relation to atmospheric conditions, 1928, VIII, 130.
Fearon, W. R. The biochemistry of urea, 1926, VI, 399.
Fibrillation, auricular, 1924, IV, 215.
Filterable viruses, 1923, III, 483.
Folin, O. Non-protein nitrogen of blood in health and disease, 1922, II, 460.
Foodstuffs, major, interconversion of, 1930, X, 349.
Forbes, A. The interpretation of spinal reflexes in terms of present knowledge of nerve conduction, 1922, II, 361.
Franklin, K. J. The physiology and pharmacology of veins, 1928, VIII, 346.
Fredericq, H. Chronaxie, 1928, VIII, 501.

G

Gall bladder, functions of, 1924, IV, 251.
Garrey, W. E. Auricular fibrillation, 1924, IV, 215.
Gasser, H. S. Contractures of skeletal muscle, 1930, X, 35.
Gastric juice, secretion of, in health and disease, 1923, III, 1.
Gay, F. P. Local resistance and local immunity to bacteria, 1924, IV, 191.
Geiling, E. M. K. The pituitary body, 1926, VI, 62.
Genetics and problem of embryonic development, 1923, III, 603.
Gesell, R. The chemical regulation of respiration, 1925, V, 551.
Goiter, distribution of iodine with special reference to, 1927, VII, 189.
Goldschmidt, S. On the mechanism of absorption from the intestine, 1921, I, 421.
Green, H. H. Perverted appetites, 1925, V, 336.
Greene, C. W. The physiology of the spawning migration, 1926, VI, 201.
Growth curve in annual plants, 1927, VII, 151.
Gunn, J. A. Cellular immunity: congenital and acquired tolerance to non-protein substances, 1923, III, 41.

H

Haldane, J. S. Acclimatisation to high altitudes, 1927, VII, 363.
Harding, V. J. Metabolism in pregnancy, 1925, V, 279.
Harvey, E. N. Recent advances in bioluminescence, 1924, IV, 639.
Hatcher, R. A. The mechanism of vomiting, 1924, IV, 479.
Heart beat, origin and conduction of, 1921, I, 1.
regulation of coronary circulation in, 1926, VI, 596.
tonus, 1927, VII, 259.
volume changes of the, 1923, III, 165.
Heat, physiological responses to, 1927, VII, 531.
Heat-regulating mechanism of the body, 1921, I, 295.
Heidelberger, M. The chemical nature of immune substances, 1927, VII, 107.
Heme pigments and cellular respiration, hemoglobin—, 1930, X, 506.
Hemoglobin and erythrocytes, regeneration of, 1929, IX, 666.
heme pigments and cellular respiration, 1930, X, 506.
significance of, 1924, IV, 329.
significance of, in submammalian forms of life, 1925, V, 596.
Henderson, V. E. The present status of the theories of narcosis, 1930, X, 171.
Henderson, Y. Physiological regulation of the acid-base balance of the blood and some related functions, 1925, V, 131.
Volume changes of the heart, 1923, III, 165.
Herrick, C. J. Morphogenetic factors in the differentiation of the nervous system, 1925, V, 112.
Hill, A. V. The mechanism of muscular contraction, 1922, II, 310.
Hines, M. On cerebral localization, 1929, IX, 462.
Hitchcock, D. I. Proteins and the Donnan equilibrium, 1924, IV, 505.
Homeostasis, physiological, organization for, 1929, IX, 399.
Hooker, D. R. Evidence of functional activity on the part of the capillaries and venules, 1921, I, 112.
Hormones in digestion, 1930, X, 282.
ovarian and placental, 1927, VII, 600.

Horrax, G. Contributions of the war to the physiology of the nervous system, 1921, I, 269.
Hoskins, R. G. The relation of the adrenals to the circulation, 1922, II, 343.
Howe, P. E. The function of the plasma proteins, 1925, V, 439.
Howell, W. H. Inhibition, 1925, V, 161.
Hunter, A. The physiology of creatine and creatinine, 1922, II, 586.
Hypertension, arterial, and hypotension, 1927, VII, 431.
Hypotension, arterial hypertension and, 1927, VII, 431.

I

Immune substances, chemical nature of, 1927, VII, 107.
Immunity, cellular, 1923, III, 41.
local, to bacteria, 1924, IV, 191.
Individuality, transplantation and, 1930, X, 547.
Inheritance of acquired characters, 1925, V, 244.
Inhibition, 1925, V, 161.
Insulin, 1924, IV, 21.
Internal secretion, 1927, VII, 288.
Intestinal absorption, 1921, I, 421.
Intestinal autointoxication, 1924, IV, 352.
Intestine, small, rôle of, in nutrition, 1930, X, 473.
Intracellular digestion, 1923, III, 552.
Iodine, distribution of, with special reference to goiter, 1927, VII, 189.
Ivy, A. C. The rôle of hormones in digestion, 1930, X, 282.

K

Katz, L. N. The significance of the T wave in the electrogram and electrocardiogram, 1928, VIII, 447.
Kendall, A. I. Bacterial metabolism, 1923, III, 438.
Kennedy, W. P. Diet and sterility, 1926, VI, 485.
Kleitman, N. Sleep, 1929, IX, 624.
Krumbhaar, E. B. Functions of the spleen (Mysterii Plenum Organon Galen), 1926, VI, 160.
Kruse, H. D. and **E. V. McCollum.** Biochemical investigation of vitamin B, 1929, IX, 126.

L

Langworthy, O. R. The control of posture by the central nervous system, 1928, VIII, 151.
Laurens, H. The physiological effects of radiation, 1928, VIII, 1.
Lee, F. C. The regeneration of nervous tissue, 1929, IX, 575.
Leukocytes, the, 1922, II, 505.
Levene, P. A. Structure and significance of the phosphatides, 1921, I, 327.
Lewis, H. B. Sulfur metabolism, 1924, IV, 394.
Light, physiological action of, 1922, II, 277.
Lillie, R. S. Transmission of physiological influence in protoplasmic systems, especially nerve, 1922, II, 1.

Loeb, L. Transplantation and individuality, 1930, **X,** 547.
Longcope, W. T. Anti-anaphylaxis and desensitization, 1923, III, 240.
Lungs, musculature of bronchi and, 1929, **IX,** 1.
Lusk, G. The physiological effect of undernutrition, 1921, I, 523.

M

MacCallum, A. B. The paleochemistry of the body fluids and tissues, 1926, VI, 316.
MacCallum, W. G. Arteriosclerosis, 1922, II, 70.
McCance, R. A. The chemistry of the degradation of protein nitrogen, 1930, X, 1.
McClendon, J. F. The distribution of iodine with special reference to goiter, 1927, VII, 189.
McCollum, E. V. *See* KRUSE and MCCOLLUM, 1929, IX, 126.
Macklin, C. C. The musculature of the bronchi and lungs, 1929, IX, 1.
McLean, F. C. Edema as a problem in physiological regulation, 1925, V, 618.
Macleod, J. J. R. Insulin, 1924, IV, 21.
The sugar of the blood, 1921, I, 208.
MacNider, W.deB. A review of acute experimental nephritis, 1924, IV, 595.
MacWilliam, J. A. Blood pressures in man under normal and pathological conditions, 1925, V, 303.
Magee, H. E. The rôle of the small intestine in nutrition, 1930, X, 473.
Mann, F. C. The functions of the gall bladder, 1924, IV, 251.
Marine, D. The present status of the functions of the thyroid gland, 1922, II, 521.
Marriott, W. McK. Anhydremia, 1923, III, 275.
Marshall, E. K., Jr. The secretion of urine, 1926, VI, 440.
Marshall, F. H. A. The internal secretions of the reproductive organs, 1923, III, 335.
Marshall, J. A. The etiology of dental caries, 1924, IV, 564.
Martin, E. G. Tests of muscular efficiency, 1921, I, 454.
Mathews, A. P. Adsorption, 1921, I, 553.
Maximow, A. A. Relation of blood cells to connective tissues and endothelium, 1924, IV, 533.
Meakins, J. Arterial hypertension and hypotension and their clinical significance, 1927, VII, 431.
Meek, W. J. The question of cardiac tonus, 1927, VII, 259.
Meek, W. J. *See* EYSTER and MEEK, 1921, I, 1.
Meigs, E. B. Milk secretion as related to diet, 1922, II, 204.
Mellanby, M. The influence of diet on the structure of teeth, 1928, VIII, 545.
Membranes, serous, physiology of, 1926, VI, 242.
Menstruation, oestrus, ovulation and, 1923, III, 457.
Metabolism, bacterial, 1923, III, 438.
basal, 1924, IV, 69.
basal, of children, 1925, V, 477.
calcium, 1928, VIII, 283.
in pregnancy, 1925, V, 279.
intermediary, of carbohydrates, 1923, III, 394.

Metabolism, mineral, and acid-base equilibrium, 1923, III, 509.
of autotrophic bacteria, 1927, VII, 85.
of developing egg, 1925, V, 1.
protein, influence of muscle work on, 1925, V, 225.
purine, 1923, III, 544.
relation of adrenal bodies to, 1924, IV, 163.
sulfur, 1924, IV, 394.
Migration, spawning, physiology of, 1926, VI, 201.
Milk secretion as related to diet, 1922, II, 204.
Miller, F. R. The physiology of the cerebellum, 1926, VI, 124.
Mineral metabolism in relation to acid-base equilibrium, 1923, III, 509.
Mirsky, A. E. *See* ANSON and MIRSKY, 1930, X, 506.
Mitchell, H. H. The nutritive value of proteins, 1924, IV, 424.
Morgan, T. H. The modern theory of genetics and the problem of embryonic development, 1923, III, 603.
Morphogenetic factors in differentiation of nervous system, 1925, V, 112.
Muscle, plain, physiology of, 1926, VI, 358.
red and white, 1926, VI, 1.
skeletal, contractures of, 1930, X, 35.
skeletal, tonus of, 1925, V, 518.
Muscle work, influence of, on protein metabolism, 1925, V, 225.
Muscular contraction, mechanism of, 1922, II, 310.
phosphorus in chemical mechanism of, 1929, IX, 432.
Muscular efficiency, 1921, I, 454.
Musculature of bronchi and lungs, 1929, IX, 1.
Myers, V. C. Chemical changes in the blood and their clinical significance, 1924, IV, 274.

N

Narcosis, 1930, X, 171.
Nash, T. P., Jr. Phlorhizin diabetes, 1927, VII, 385.
Needham, D. M. Red and white muscle, 1926, VI, 1.
Needham, J. The metabolism of the developing egg, 1925, V, 1.
Nephritis, acute experimental, 1924, IV, 595.
Nerve, excitation and conduction in, 1922, II, 1.
Nerve impulse, conduction of, 1926, VI, 547.
Nervous system, central, in control of posture, 1928, VIII, 151.
contributions of the War to the physiology of, 1921, I, 269.
differentiation of, 1925, V, 112.
Nervous tissue, regeneration of, 1929, IX, 575.
Neutrality regulations in the body, 1923, III, 295.
Nitrogen, non-protein, of blood in health and disease, 1922, II, 460.
protein, chemistry of degradation of, 1930, X, 1.
Nutrition, rôle of small intestine in, 1930, X, 473.
under-, effects of, 1921, I, 523.
Nutritive value of proteins, 1924, IV, 424.

O

Oestrus, ovulation and menstruation, 1923, **III,** 457.
Opie, E. L. Intracellular digestion. The enzymes and anti-enzymes concerned, 1922, **II,** 552.
Organic compounds, foreign, fate of, in animal body, 1922, II, 238.
Osborne, T. B. *See* VICKERY and OSBORNE, 1928, VIII, 393.
Ovarian and placental hormones, 1927, **VII,** 600.
Ovulation and menstruation, oestrus, 1923, **III,** 457.
Oxidases, aerobic, 1928, **VIII,** 245.
Oxidations, physiological, 1921, **I,** 394.

P

Paleochemistry of body fluids and tissues, 1926, **VI,** 316.
Parathyroid glands, 1927, **VII,** 499.
Park, E. A. The etiology of rickets, 1923, **III,** 106.
Parks, G. S. *See* BAAS-BECKING and PARKS, 1927, VII, 85.
Percival, G. H. *See* STEWART and PERCIVAL, 1928, VIII, 283.
Perverted appetites, 1925, **V,** 336.
Phlorhizin diabetes, 1927, **VII,** 385.
Phosphatides, structure and significance of, 1921, **I,** 327.
Phosphorus in chemical mechanism of muscular contraction, 1929, **IX,** 432.
Photo-electric currents in the eye, 1921, **I,** 84.
Pike, F. H. The function of the vestibular apparatus, 1923, III, 209.
Pituitary body, 1926, **VI,** 62.
Placental hormones, ovarian and, 1927, **VII,** 600.
Plants, annual, growth curve in, 1927, **VII,** 151.
Plasma proteins, function of, 1925, **V,** 439.
Posture, control of, by central nervous system, 1928, VIII, 151.
Pregnancy, metabolism in, 1925, **V,** 279.
Protein, enzymatic synthesis of, 1930, **X,** 110.
metabolism, influence of muscle work on, 1925, **V,** 225.
nitrogen, chemistry of degradation of, 1930, **X,** 1.
Proteins and the Donnan equilibrium, 1924, **IV,** 505.
nutritive value of, 1924, **IV,** 424.
physical chemistry of, 1925, **V,** 349.
plasma, function of, 1925, **V,** 439.
structure of, 1928, **VIII,** 393.
Protoplasmic systems, transmission of physiological influence in, 1922, **II,** 1.
Pulmonary circulation, regulation of, 1921, **I,** 239.
Purine metabolism, 1923, **III,** 544.

R

Radiation, physiological effects of, 1928, **VIII,** 1.
Roentgen, physiological effects of, on normal body tissues, 1928, **VIII,** 92.
Ranson, S. W. Afferent paths for visceral reflexes, 1921, **I,** 477.
Raper, H. S. The aerobic oxidases, 1928, **VIII,** 245.

Rapport, D. The interconversion of the major foodstuffs, 1930, **X**, 349.
Reflexes, spinal, 1922, **II**, 361.
visceral, afferent paths for, 1921, **I**, 477.
Regeneration of hemoglobin and erythrocytes, 1929, **IX**, 666.
of nervous tissue, 1929, **IX**, 575.
Reproductive organs, internal secretions of, 1923, **III**, 335.
Resistance and immunity to bacteria, 1924, **IV**, 191.
Respiration, cellular, 1930, **X**, 506.
chemical regulation of, 1925, **V**, 551.
Respiratory quotient, 1929, **IX**, 61.
Reticulo-endothelial system, 1926, **VI**, 504.
Rich, A. R. The formation of bile pigment, 1925, **V**, 182.
Richardson, H. B. The respiratory quotient, 1929, **IX**, 61.
Rickets, etiology of, 1923, **III**, 106.
Robscheit-Robbins, F. S. The regeneration of hemoglobin and erythrocytes, 1929, **IX**, 666.
Rose, W. C. Purine metabolism, 1923, **III**, 544.
Rous, P. Destruction of the red blood corpuscles in health and disease, 1923, **III**, 75.
Rowntree, L. G. The water balance of the body, 1922, **II**, 116.

S

Sabin, F. R. Bone marrow, 1928, **VIII**, 191.
On the origin of the cells of the blood, 1922, **II**, 38.
Sacks, B. The reticulo-endothelial system, 1926, **VI**, 504.
Sandiford, I. *See* **Boothby and Sandiford,** 1924, **IV**, 69.
Schmidt, C. L. A. The extra-hepatic functions of bile, 1927, **VII**, 129.
Schneider, E. C. Physiological effects of altitude, 1921, **I**, 631.
Secretion, internal, 1927, **VII**, 288.
of gastric juice, 1923, **III**, 1.
Secretions, internal, of reproductive organs, 1923, **III**, 335.
Sense organs, mechanism of, 1930, **X**, 336.
Serous membranes, physiology of, 1926, **VI**, 242.
Sex, determination of, in animals, 1926, **VI**, 28.
Shaffer, P. A. Intermediary metabolism of carbohydrates, 1923, **III**, 394.
Sheard, C. Photo-electric currents in the eye, 1921, **I**, 84.
Sherman, H. C. The vitamins, 1921, **I**, 598.
Sherwin, C. P. The fate of foreign organic compounds in the animal body, 1922, **II**, 238.
Shohl, A. T. Mineral metabolism in relation to acid-base equilibrium, 1923, **III**, 509.
Simon, C. E. The filterable viruses, 1923, **III**, 483.
Skeletal muscle, tonus of, 1925, **V**, 518.
Sleep, 1929, **IX**, 624.
Sollmann, T. The pharmacology of the autonomic system, 1922, **II**, 479.
Spawning migration, physiology of, 1926, **VI**, 201.
Spinal reflexes, 1922, **II**, 361.
Spleen, functions of, 1926, **VI**, 160.

Stammers, A. D. A review of recent advances in the study of blood sugar and diabetes, 1926, VI, 630.
Statistical methods, application of, in physiology, 1929, IX, 275.
Sterility, diet and, 1926, VI, 485.
Stewart, C. P. and **G. H. Percival.** Calcium metabolism, 1928, VIII, 283.
Stewart, G. N. Adrenalectomy and the relation of the adrenal bodies to metabolism, 1924, IV, 163.
Stomach, digestive work of, 1928, VIII, 365.
Sugar of the blood, 1921, I, 208.
Sulfur metabolism, 1924, IV, 394.
Sundstroem, E. S. The physiological effects of tropical climate, 1927, VII, 320.
Suspension stability of blood, 1929, IX, 241.
Swingle, W. W. The determination of sex in animals, 1926, VI, 28.

T

T wave, significance of, in electrogram and electrocardiogram, 1928, VIII, 447.
Talbot, F. B. Basal metabolism of children, 1925, V, 477.
Teeth, influence of diet on structure of, 1928, VIII, 545.
Thyroid gland, functions of, 1922, II, 521.
Tissue culture and cell physiology, 1924, IV, 1.
Tissues, connective and endothelium, relation of blood cells to, 1924, IV, 533.
Tonus, cardiac, 1927, VII, 259.
of skeletal muscle, 1925, V, 518.
Transfusion problem, 1927, VII, 1.
Transplantation and individuality, 1930, X, 547.

U

Undernutrition, physiological effects of, 1921, I, 523.
Urea, biochemistry of, 1926, VI, 399.
Urine, secretion of, 1926, VI, 440.

V

Van de Sande-Bakhuyzen, H. L. and **C. L. Alsberg.** The growth curve in annual plants, 1927, VII, 151.
Van Slyke, D. D. The carbon dioxide carriers of the blood, 1921, I, 141.
Veins, physiology and pharmacology of, 1928, VIII, 346.
Venous pressure and its clinical applications, 1926, VI, 281.
Venules, functional activity of capillaries, and, 1921, I, 112.
Vernon, H. M. Industrial fatigue in relation to atmospheric conditions, 1928, VIII, 130.
Vestibular apparatus, function of, 1923, III, 209.
Vickery, H. B. and **T. B. Osborne.** A review of hypotheses of the structure of proteins, 1928, VIII, 393.
Vincent, S. Current views on "internal secretion," 1927, VII, 288.
Viruses, filterable, 1923, III, 483.
Visceral reflexes, afferent paths for, 1921, I, 477.
Vitamin B, biochemical investigation of, 1929, IX, 126.

Vitamins, the, 1921, **I,** 598.
Voegtlin, C. The pharmacology of arsphenamin (salvarsan) and related arsenicals, 1925, **V,** 63.
Vomiting, mechanism of, 1924, **IV,** 479.
von Oettingen, W. F. The absorption, distribution and excretion of bismuth, 1930, **X,** 221.

W

Warren, S. L. The physiological effects of Roentgen radiation upon normal body tissues, 1928, **VIII,** 92.
Wasteneys, H. and **H. Borsook.** The enzymatic synthesis of protein, 1930, **X,** 110.
Water balance of the body, 1922, **II,** 116.
Weed, L. H. The cerebrospinal fluid, 1922, **II,** 171.
Wells, H. G. The present status of the problems of anaphylaxis, 1921, **I,** 44.
Whipple, G. H. The origin and significance of the constituents of the bile, 1922, **II,** 440.
Wiggers, C. J. The regulation of the pulmonary circulation, 1921, **I,** 239.
Wilson, D. W. Neutrality regulations in the body, 1923, **III,** 295.
Work, muscle, influence of, on protein metabolism, 1925, **V,** 225.

THE BIOCHEMICAL JOURNAL

EDITED FOR THE BIOCHEMICAL SOCIETY BY
HAROLD WARD DUDLEY and ARTHUR HARDEN
With the Assistance of an Editorial Committee

Vol. XXIV, No. 2. 1930. Price 20s. net

CONTENTS

Obituary Notice.

The effect of cereal extracts on blood-calcium. By L. Mirvish.

The tyrosinase-tyrosine reaction. VII. The action of tyrosinase on certain substances related to tyrosine. By W. L. Dulière and H. S. Raper. (With one figure.)

Sulphur in organic and inorganic combination in pasture grasses. By H. A. A. Aitken.

Surface films of batyl, chimyl and selachyl alcohols. By B. C. J. G. Knight. (With two figures.)

The decarboxylation of pectin. By F. V. Linggood.

The composition of the mixed fatty acids present in the glycerides of cod-liver and certain other fish-liver oils. By K. D. Guha, T. P. Hilditch and J. A. Lovern.

The effect of glutathione on the determination of blood-sugar. By F. K. Herbert, M. C. Bourne and J. Groen. (With one figure.)

The non-sugar reducing substances of human blood, with special reference to glutathione. By F. K. Herbert and M. C. Bourne.

On the catalysis of the oxidation of cysteine and thioglycollic acid by iron and copper. By K. A. C. Elliott. (With fourteen figures.)

A study of the composition of human milk in the later periods of lactation and a comparison with that of early milk. By S. T. Widdows, M. F. Lowenfeld, M. Bond and E. I. Taylor.

Fermentation by yeast preparations. By A. Harden and M. G. Macfarlane. (With two figures.)

Phosphoric esters in alcoholic fermentation. II. Pyrophosphate in yeast preparations. By E. Boyland. (With one figure.)

Note on the determination of total calcium in blood-serum. By J. Patterson.

Studies on gelatin. XI. Diamino-nitrogen of gelatin. By K. V. Thimann. (With three figures.)

The precipitation of the basic amino-acids of proteins with phosphotungstic acid. By K. V. Thimann. (With Plate I and three figures.)

Investigations on the hydrolysis products of fish muscle. I. The diamino-nitrogen of cod muscle. By J. C. Kernot, J. Knaggs and N. E. Speer.

The influence of the hypophysis on metabolism, growth and sexual organs of male rats and rabbits. II. Influence of extracts of hypophysis on the body weight, weight of fat, of sexual organs and of endocrine organs of rats. By V. Korenchevsky.

The Hagedorn-Jensen method applied to various sugars. Relation of reducing power to configuration. By H. Sobotka and M. Reiner. (With one figure.)

A note on the oxygen consumption of nerve in the presence of glucose and galactose. By M. Sherif and E. G. Holmes. (With two figures.)

Studies on pectin. IV. The oxidation of pectin by Fenton's reagent and its bearing on the genesis of the hemicelluloses. By A. G. Norman and F. W. Norris.

Xanthine oxidase in the avian embryo. By E. J. Morgan.

Factors affecting the catalytic action of copper in the oxidation of cysteine. By C. A. Elvehjem. (With eleven figures.)

The action of salts on fumarase. I. By P. J. G. Mann and B. Woolf. (With six figures.)

The chemestry of oestrin. III. An improved method of preparation and the isolation of crystalline material. By G. F. Marrian. (With Plate II.)

Studies on antiglyoxalase. I. The action of pancreatic extract on phenylglyoxal. By J. O. Giršavičius. (With two figures.)

The alleged contamination of caroten by vitamin A. By N. S. Capper. (With one figure.)

The isolation of l-thyroxine from the thyroid gland by the action of proteolytic enzymes. By C. R. Harington and W. T. Salter.

The properties of pure glutathione. By N. U. Meldrum and M. Dixon. (With twenty-three figures.)

Further experiments on cancer-producing substances. By E. L. Kennaway.

The spectra of cancer-producing tars and oils and of related substances. By I. Hieger. (With Plates III and IV.)

Oxidation-reduction potentials of cultures of haemolytic streptococci. I. By L. F. Hewitt. (With eleven figures.)

Studies in gas production by bacteria. I. Apparatus for the measurement of the rate of gas production. By J. A. Cranston. (With three figures.)

Studies in gas production by bacteria. II. Denitrification and bacterial growth phases. By B. Lloyd and J. A. Cranston. (With ten figures.)

The production of hydrogen sulphide by animal tissues. By E. Sluiter. (With seven figures.)

A redetermination of the titration dissociation constants of arginine and histidine with a demonstration of the zwit erion constitution of these molecules. By T. W. Birch and L. J. Harris. (With two figures.)

Now ready. Index of Authors and Subjects to Volumes XI–XX. 10s. net. Postage 4d. extra.
Further particulars of the Journal and subscription prices will be sent on request.

CAMBRIDGE UNIVERSITY PRESS
FETTER LANE, LONDON, E.C. 4, ENGLAND

PHYSIOLOGICAL ABSTRACTS

Monthly, price 5s. net. Annual Subscription, post free, 42s

This Journal is issued by the PHYSIOLOGICAL SOCIETY, acting in co-operation with numerous physiological organisations in Great Britain, America, and other countries. The Editor, Prof. J. MELLANBY, is assisted by a staff of competent abstractors both at home and abroad.

The Journal aims at issuing promptly abstracts of the papers published throughout the world, in physiological and allied sciences (including Plant Physiology).

A number is published at the beginning of each month.

Volume X began with the April (1925) issue.

Subscriptions are only taken for April to March of the next year, and are payable in advance.

Back numbers, excepting some which are out of print, may be obtained from the Publishers, or any Bookseller. An extra charge is made for some numbers the stock of which is nearly exhausted. Prices on application.

Binding Cases, price 2s. net, are supplied by the Publishers, who can also arrange for binding; prices on application.

PUBLISHED BY

H. K. LEWIS & CO., Ltd.

136 Gower Street LONDON, W. C. 1

Publishing Office, 28 Gower Place, London, W. C. 1

SUBSCRIPTIONS MAY BE PAID THROUGH ANY BOOKSELLER

INDEX

AMERICAN JOURNAL OF PHYSIOLOGY

An Index to Volumes 61 to 90 inclusive of the American Journal of Physiology will be published about December, 1930, the price of which will be $4.00 per copy if ordered in advance.

A few copies of the Index to Volumes 1 to 30 inclusive (price $4.00) and of the Index to Volumes 31 to 60 inclusive (price $2.50) are still available.

Orders should be sent to the American Journal of Physiology, 19 W. Chase Street, Baltimore, Md.

PHYSIOLOGICAL REVIEWS

Tentative Contents of Volume XI, 1931

An Index to Volumes I to X inclusive will be published in the January issue

R. W. GERARD: Metabolism of Nerve
PERCIVAL BAILEY: Functions of the Hypothalamus
E. U. STILL: Secretin
W. O. FENN: Energy Changes in Muscular Contraction
W. F. PETERSEN: Disease and Constitution
R. H. JAFFE: The Reticulo-Endothelial System in Immunity
W. H. RUSHTON: The Nature of Electrical Excitation
T. H. MILROY: The Present Status of the Chemistry of Skeletal Muscular Contraction
J. ARGYLL CAMPBELL: The Tension of Gases in Tissue
E. WALDSCHMIDT-LEITZ: The Mode of Action and Differentiation of Proteolytic Enzymes
H. A. SPOEHR: Photosynthesis
C. H. BEST AND E. W. MCHENRY: Histamine
A. D. HIRSCHFELDER AND R. N. BIETER: Local Anesthetics: Relation of Constitution and Action
CARL VOEGTLIN: Testing of Trypanocidal Agents
OSCAR RIDDLE: Factors in the Development of the Secondary Sex Characteristics
ERIC PONDER: Hemolysis

Subscriptions may be sent to D. R. Hooker, Managing Editor, 19 W. Chase Street, Baltimore, Md. $6.00 per volume, domestic. $6.50 per volume, foreign.

Physiological Research Periodicals, complete files, back volumes and odd copies for sale. We purchase Medical and Scientific Magazines.

B. LOGIN & SON
29 EAST 21ST STREET, NEW YORK CITY